REATIONS OF SOME CYCLIC NITRONES

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MASTER OF SCIENCE.

by

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Statement

I wish to thank Professor A.H. Hassly for the opportunity to work in the Chemistry Department, School of General Studies, Australian National University, under the guidance of Dr. S.C. Crow, for initiating me into research, for their patient guidance and for valuable advice.

I am also very grateful to Dr. C.P. Whittle for many helpful discussions.

My thanks are also due to all other members of the Department for invaluable cooperation.

Lalitkala Subrahmanyan

May, 1966
I wish to thank Professor A.N. Hambly for the opportunity to work in the Chemistry Department, School of General Studies, Australian National University.

I am greatly indebted to my supervisors, Dr. R.F.C. Brown and Professor W.D. Crow, for initiating me into research, for their patient guidance and for valuable advice.

I am also very grateful to Dr. C.P. Whittle for many helpful discussions.

My thanks are also due to all other members of the Department for invaluable co-operation.
Certain aspects of the reactivity of cyclic α-ketonitrones has been studied, including their substitution reactions (both nucleophilic and radical) and the oxidative dimerisation of one of them under the influence of chromate ion. The reactions observed are interpreted in the light of the dual polarisability of the azomethine-N-oxide grouping, viz -

\[
\begin{align*}
R' + R & \xrightleftharpoons[\text{(a)}]{\text{(b)}} R' + R \\
R'' + N - O & \xrightarrow[\text{(a)}]{\text{(b)}} C = N - O
\end{align*}
\]

A study has been made of the rearrangements of one of the α-ketonitrones to the isomeric amide under conditions of both acid and base catalysis. With acetic anhydride, acylation occurred as well as isomerisation of the amide and the structures of the products arising from such reactions have been examined. Mechanisms are proposed for the transformations observed.

The mass spectra of the acylation products and certain deuterated derivatives have been interpreted in the light of the structures assigned.
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\( \alpha-N\)-di phenylnitroline  \( \alpha\)-phenyl - \( \alpha\)-methyl - \( \alpha\)-phenyl nitroline

\( \text{VII} \)

\( \text{VIII} \)

\( \text{IX} \)

Aspergillie acid
INTRODUCTION

The term "nitrone" was introduced by Pfeiffer to describe the general class of compounds containing the structural feature \( \text{C} = \text{N} \rightarrow \text{O} \), thus the simplest open chain nitrones are the oxime N-ethers first prepared by Beckmann in 1880. [e.g. : I and II]

Structure of nitrones

The oxaziridine structure III was initially proposed for these compounds, but was soon replaced by the open chain structure as a result of the work of Brady and the isolation of geometric isomers. Failure to resolve the bromocamphorsulphonate of IV (the oxaziridine structure would require optical isomers) led to similar conclusions and these have been fully confirmed by the synthesis of the oxaziridines as entities quite distinct from the isomeric nitrones.

The formal analogy between the nitrone structure (a) and that of a protonated ketone or aldehyde (b) leads to a simple explanation of the general reactivity of nitrones as C-electrophile as in the reaction V. The same sort of mobility of \( \pi \) electrons occurs in the case of enamine salts (c) also. The electrophilic character of the carbon atoms in these systems also facilitates anion formation at the \( \alpha \) carbon atoms.

Although the charge on the oxygen atom in (b) and that on the nitrogen atom in (c) can be removed, this is not possible in the case of nitrones. The analogous electron shifts here lead to nucleophilic reactivity at the nitrone carbon VI. This dual activity of nitrones can be observed in some of their chemical reactions such as dimerisation and 1,3 cycloadditions.

Aromatic N-oxides like pyridine N-oxide VII and N-oxides of other heterocyclic compounds (e.g. VIII and IX) contain the \( \text{C} = \text{N} \) of the
Isoxazoline 2-oxide  

Furoxan  

2-phenyl isatogen

\[ \begin{align*}
  \text{Isoxazoline} & \quad \text{Furoxan} \\
  \text{2-oxide} & \quad \text{2-phenyl isatogen}
\end{align*} \]

\[ \text{XII} \quad \text{XIII} \quad \text{XIX} \]

\[ \begin{align*}
  (\text{CH}_3)_2\text{C-CH}_2\text{-C-CH}_3 & \quad \text{C}_6\text{H}_5-\text{N-OH}+\text{N-O}^- \\
  & \quad \text{C}_6\text{H}_5
\end{align*} \]

\[ \text{XX} \quad \text{XXI} \quad \text{XXIV} \quad \text{XXIII} \]

\[ \begin{align*}
  \text{XX} & \quad \text{XXI} \\
  \text{XX} & \quad \text{XXI}
\end{align*} \]
azomethine N-oxide as part of their aromatic ring. However, the mere presence of an azomethine N-oxide group in a compound does not necessarily mean that it will show the properties and reactions of a nitrone. The delocalization of the positive charge on the nitrogen atom of the nitrone, which controls most of the typical reactions of nitrones, is confined to the C atom of the azomethine N-oxide group X. As a result, nitrones are more easily reduced and more highly polarized than heterocyclic amine oxides in which a high degree of delocalization leads to greater stability of the system. Colonna considered heterocyclic amine oxides to be aldonitrones on the basis of the reactions of quinoline N-oxides with KCN to give 2 cyanoquinoline XI. Similarly, pyridine N-oxide reacts with phenylmagnesium bromide to give a phenylpyridine. However, this interpretation ignores the other marked differences that exist between heterocyclic amine oxides and aldonitrones, which are the result of the greater delocalization in the former. For similar reasons, compounds in which the N of the azomethine N-oxide group is attached to an atom with an unshared pair of electrons (XII, XIII) are best not regarded as nitrones because the additional electron shifts can affect the polarisation of the group. Compounds like isatogens (XIX) and other α-phenyl substituted nitrones (XX), however, show characteristic reactions of nitrones (e.g., 1, 3 cycloaddition) despite the presence of the aromatic groups, because the stability of the aromatic system leads to the retention of the positive charge on the nitrone group without delocalization. This restricts the resonance forms of the nitrone group to the canonical forms X.

The presence of a nitrone group appears to facilitate dimerisation
in aliphatic nitrones, and all those described in early work were dimers, such as that (XXI) resulting from oxidation of N-hydroxyperidine, and the aldol type dimer XXII obtained from acetone and phenylhydroxylamine. 

Δ⁻¹-pyrroline oxides of the type XXIII and XXIV were the first monomeric alicyclic nitrones to be isolated and correctly formulated.

Methods of synthesis

A number of methods are available for the synthesis of nitrones.

From N N disubstituted hydroxylamines:

The commonly used method is to oxidise substituted hydroxylamines. This method can be used only when at least one of the C-atoms attached to the nitrogen carries a hydrogen atom.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{H} & \quad \text{OH} \\
\text{C} \quad \text{N} \quad \text{R}^n \\
& \quad \text{H} \\
\end{align*}
\]

Cupric acetate, yellow mercuric oxide, active lead oxide, K₃Fe(CN)₆, KMnO₄, H₂O₂ etc. have been used as oxidising agents. Air oxidation has also been used. Aqueous cupric salt solution accelerates the uptake of oxygen markedly in an alkaline medium. The mechanism of the oxidation was considered to involve both ionic and radical species. The initially produced radical nitrosyl compound (x) containing a hydrogen could undergo oxidation very easily to a stabilised ion radical (y). Loss of the unpaired electron from this ion radical to the metal catalyst could result in a nitrone.
From N-substituted hydroxylamines by addition with carbonyl compounds:

\[
\begin{align*}
R' \quad \text{N} & \quad R'' \quad \text{O} \quad \longrightarrow \quad R' \quad \text{N} & \quad R'' \quad \text{O} \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \longrightarrow & \quad \text{H} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

\(\Delta^1\)-Pyrroline 1-oxides can be prepared by this method. The \(\gamma\)-nitroketones or nitroaldehydes prepared by Michael's addition reaction undergo reductive cyclization on treating with a mild reducing agent (e.g., zinc and \(\text{NH}_4\text{Cl}\)).
From oximes

Open chain nitrones are prepared by N-alkylation of oximes.20 The disadvantage of this method is that alkylation at both O and N gives a mixture of products.

\[
\begin{align*}
\text{R'} \quad \text{C} = \text{N - OH} & \quad + \quad \text{RX} \\
\text{R''} & \quad \rightarrow \quad \text{C} = \text{N - O - R} + \text{C} = \text{N - O} + \text{HX}
\end{align*}
\]

From aromatic nitroso-compounds:

Nitrones can be prepared by the action of aromatic nitroso-compounds on reagents containing active methyl or methylene groups.21 The initial step is to form a N, N-di substituted hydroxylamine by a base catalysed addition of the reagent to the nitroso-compound. This intermediate can either loose water to form an anil (A) or can be oxidised with excess of nitroso-compound to yield a nitrone (B).

Kroehnke22 synthesis of nitrones consists of using pyridinium salts as the
active methylene reagents. Pyridinium salts can be prepared by King’s reaction and on reacting with nitroso-compounds in presence of a base yields a nitrone.

\[
\text{Ar-CH}_2^+ \xrightarrow{\text{Ar}^+\text{NO}} \text{ArCH} = \text{NAr}^+ + \text{HX} + \text{Ar-CH}_2^+\]

Properties of nitrones

Spectroscopically, the nitrone group can be detected in the infrared region by the strong \(\text{N} \rightarrow \text{O}\) stretching frequency at about 1170 to 1280 cm\(^{-1}\), and \(\text{C} = \text{N}\) stretching absorption between 1540 and 1620 cm\(^{-1}\). \(\Delta^1\)-pyrroline-1-oxides exhibit strong absorption ranging from 1570 to 1620 cm\(^{-1}\) depending upon the substitution at the \(\alpha\) position. The shift of the frequency from aldo to ketonitrones is in the opposite direction to that found in the carbonyl compounds (aldehydes 1745 to 1720 cm\(^{-1}\); ketones 1725 to 1705 cm\(^{-1}\)). In the ultraviolet region, the \(\text{C} = \text{N} \rightarrow \text{O}\) chromophore has a single absorption maximum at 229 to 235 μ. The position of the absorption maximum may be shifted when the nitrone function is conjugated with other functional groups.

The name nitrone itself indicates its relationship with ketones. Thus, addition of nucleophilic reagents like Grignard reagents and substituted amines takes place as in the case of aldehydes and ketones. The electrophilic activity can, however, be noticed at the same site.
indicating the back polarisation of the system. The two polarised forms of the nitroene group can be represented as follows:

Most of the reactions of nitrones can be explained on the basis of the polarised structure A, but in the case of some reactions B appears to be the reactive form. This is exemplified by the following reactions of 5, 5-dimethyl-1-pyrroline-oxide with ethyl acrylate. The mobility of \( \pi \) electrons in the nitroene system will enable formation of two different adducts (C and D), through the two forms (A and B) respectively. Their formation depends upon the polarised state or the polarisability of the reactants.

(1) At room temperature -
Other cycloaddition reactions with alkenes, conjugated alkenes, dienes, unsaturated alcohols and \( \alpha, \beta \) unsaturated carbonyl compounds are also known. In general, the reaction occurs more readily with conjugated systems. In all these, 1:3 cycloaddition with nitrone occurs to form cyclic systems. The addition need not be steriospecific and with an unsymmetrically substituted unsaturated compound sterioisomeric compounds are often obtained.

Nitrones are easily rearranged to the isomeric amides on treating with reagents like phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride, thionyl chloride, sulphur dioxide, acetic anhydride, acetyl chloride etc., a reaction analogous to the Polonovski rearrangement, although the mechanism need not be the same.

The same effect can also be obtained by photolysis. Oxizarin is an intermediate.
Reduction with metal borohydrides occur in the same way as with carbonyl compounds and leads to hydroxylamines.\(^{23}\) Deoxygenation of nitrones has been achieved with a variety of reducing agents like zinc dust and acetic acid, sulphur dioxide,\(^{23}\) triphenyl phosphine etc.\(^{29}\)

Nitrones appear to dimerise readily. The dual nature of the nitro group allows 1, 3 cycloaddition involving the two forms to yield a cyclic dimer.\(^9\)

\[\text{[Cyclic dimer]}\]

Aldol type dimers can also be obtained in the presence of active hydrogens on the α-carbon atom of the nitro group, the nitro itself acting as the nucleophile.\(^{30}\)
APPROXIMATE HALF-LIVES FOR EXCHANGE IN D₂O/BASE AT 33°C

NaOD  
0.8M  
>20hr.

0.2M
K₂CO₃  
~20min.  
~20min.

0.2M  
O₂M  
15min.

0.04M  
1hr.  
1hr.

0.006M  
15min.

Reflux  
Et₃N, EtOD;  
Isolate.

4 >> 2 > 6  
Sternhell 1964.

TABLE I.
The resemblance of the nitrone group to the carbonyl group extends also to the conversion of the adjacent methyl group to a carbonyl group during oxidation. Thus, oxidation of the nitrone XXIII with selenium dioxide gave a carbonyl compound which rearranged to an α-ketonitrone XXV on treatment with acid.

\[ \text{XXIII} \rightarrow \text{XXV} \]

An isomer of the above nitrone (XXVI) [6, 6 dimethyl - 5, 6 dihydro - 3, 4 [H] pyridone - 1 - oxide] has now been prepared by a similar method and the present work is concerned with the study of the reactions of these α-ketonitrones. Some reactions of these compounds carried out by Brown (unpublished) are described first as they could help to explain the reactions studied in the present investigations. Nitrones in general resemble carbonyl compounds in having activated H atoms at the α-carbon atoms. In \( \Delta^1 \)-pyrroline oxides, positions 2 and 3 are both of comparable acidity, thus the action of ethereal triphenylmethyl sodium affords a
2,3' normal aldol type dimer whereas sodamide in liquid ammonia gives the 2,2' dimer. The latter reaction was found to proceed through an anion intermediate.

This explanation is further supported by the deuterium exchange reactions on 4, 5, 5 - Trimethyl - $\Delta^1$ - pyrroline-1- oxide (XXIV). Exchange at 2 positions 2 and 3 was observed when potassium carbonate was used as catalyst, but the 2 position exchanged at a faster rate. Comparable reactive centres can also be predicted in the case of ketonitrones and a qualitative estimation of the exchange reactions on these compounds was carried out by nuclear magnetic resonance spectrometry; the results are shown in Table I.

The 5, 5 - dimethyl ketonitrone XXV, which exchanges at all positions
much faster, presumably reacts in the following way:

![Chemical diagram]

This mechanism for the exchange reactions explains the observed failure of the 6, 6-dimethyl ketonitrone XXVI to exchange at position 2.
NUCLEOPHILIC ADDITION REACTIONS OF a KETONITRONES

In nucleophilic addition reactions, the nitrone group behaves as an "extended" carbonyl group with addition taking place at the ends of the system. Addition of phenylhydrazine or semicarbazide to aryl substituted open chain nitrones led to a derivative of the parent carbonyl compound with the separation of the hydroxylamino group. In cyclic systems like isatogens which contain the nitrone group conjugated with a carbonyl group, 1, 3 addition was found to be more common though quinonoid character can also be noticed. Among the aliphatic nitrones Δ1-pyrroline oxides were found to undergo addition smoothly with CN−, Grignard reagents and anions of nitroalkanes.

Although the 1, 3 - additions are presumably initiated by the positively charged nitrogen and it suffers a change in valence state, no attack occurs at this site. Therefore the behaviour of the C = O and the C = N → O groups of the ketonitrones with nucleophilic reagents will be similar. The attack of nucleophilic reagents on a carbonyl group depends in part on the availability of the lone pairs of the attacking agent and in part on the extent of the electron deficiency at the carbonyl C atom. Phenylhydrazine reacts with ketonitrones XXV and XXVI, condensing at the carbonyl group to give phenylhydrazones. However, the reaction with hydrazine was different; the nitrone XXVI gave a crystalline hydrazone which was oxidised with active MnO₂ to the corresponding diazonium salt. This was converted to a 3, 5 dinitrobenzoate by reacting with 3, 5 dinitrobenzoic acid. The NMR spectrum of this ester revealed that the product might be a rearranged five membered ring (XXVII) rather than a
The spectrum of the ester was similar to that of the parent ketonitrone at the high field region with a sharp singlet (6H) at \( \tau 8.55 \) followed by a set of two triplets (2H each) representing an \( A_2B_2 \) system. The broad singlet (2H) at \( \tau 4.65 \) suggested that the product had structure XXVII and not XXVIIa; the latter would have shown two structurally different protons at C-2 and C-3. The chemical shift of this peak at \( \tau 4.65 \) is consistent with the presence of a \( CH_2 \) group, which supports the structure XXVII. The broadening of this peak could be due to the long range coupling with the methylene protons at C-3 in XXVII. The singlet for the \( gem \) dimethyl group also supports the above structure, for the addition of a bulky group \([O-CO-C_6H_3(NO_2)_2]\) would be expected to result in non-equivalence in the \( gem \) - dimethyl group. Presumably, the rearrangement might have taken place in the formation of the hydrazone itself. The NMR spectrum of the hydrazone of the \( \alpha \) ketonitrone XXV gave the chemical shift of the ethylenic proton at \( \tau 2.55 \), while that of the \( gem \)-dimethyl group
appeared at $\tau$ 8.87 again as a singlet. On the other hand, the
dinitrophenylhydrazone of the same isomer gave different absorption lines
for the two methyl protons of the gem - dimethyl group ($\tau$ 8.71, $\tau$ 8.8)
as well as for the protons of one of the methylene groups ($\tau$ 7.4, $\tau$ 7.5),
showing it to be a six membered ring. Moreover, the phenylhydrazine
derivatives with five-membered structure were obtained from the nitrone
aldehydes XXV$a$ and XXVII. These products were different from the products
obtained from a ketonitrone XXV and XXVI, both in colour and in melting
points. The NMR spectra of the DNP derivatives of the five-membered group
did not show any non-equivalence of the gem - dimethyl group, presumably
being planar.

\[ \text{CH}_3 \quad \text{CH}_3 \] \[ \text{CH}_3 \quad \text{CH}_3 \] \[ \text{CHO} \quad \text{H}_2\text{N}\cdot\text{NHR} \] \[ \text{CH}_3 \quad \text{CH}_3 \] \[ \text{CH} = \text{N}\cdot\text{NHR} \]

The rearrangement could be explained by assuming that the initial attack
is at the C atom of the nitrone group. The increased electrophilic
reactivity of this C atom, as compared to that of the carbonyl group,
might be attributed to the inductive effects of the two polarised groups
bonded to it ($N - O$ and $C^+ - O^-$). The initial reaction of the nucleo-
philic reagents would be to attack at the most electron deficient position,
C-6 in this case. Rearrangements following the initial attack might
prevent further attack at the carbonyl C atom. The carbonyl O is possibly
involved in the cyclization of the rearranged product resulting in a ring
contraction. The reactions with hydrazine can be formulated as follows -

\[
\begin{align*}
\text{CH}_3\text{N}_2\text{O} & + \text{H}_2\text{N-NH}_2 & \rightarrow & \text{CH}_3\text{N}_2\text{O} + \text{H}_2\text{N-NH}_2 \\
\text{CH}_3\text{N}_2\text{O} & + \text{H}_2\text{N-NH}_2 & \rightarrow & \text{CH}_3\text{N}_2\text{O} + \text{H}_2\text{N-NH}_2
\end{align*}
\]

The reaction with dinitrophenylhydrazine, which is acid catalysed, probably is initiated by protonation at the carbonyl oxygen.

The reaction of these α-ketonitrone with hydrazine was complicated. The hydrazone formed by the α-ketonitrone XXV was not stable and the reaction often failed to lead to crystalline derivative. Careful adjustments of experimental conditions, however, gave a small amount of crystalline product. Only intractable products resulted when it underwent oxidation followed by treatment with 3, 5 dinitrobenzoic acid.
ARYLATION OF NITRONES

The arylation of conjugated unsaturated systems using diazonium halides with copper salt catalysis was first described by Meerwein. He found that double bonds activated by electron attracting groups such as carbonyl, cyano - and phenyl were easily arylated. Olefins of a wide range of structural complexity have been arylated, the union of the aryl group usually taking place at the carbon β - to the activating group, either by substitution of a β-hydrogen or by addition of Ar and Cl to the double bond.

\[
RCH = CR'X + ArN_2^+Cl^- \rightarrow ArCR = CR'X + ArCHR - CR'XCl
\]

In the case of multiply activated olefins, the nature of the product formed would be determined by the stabilisation of the intermediate radical.

\[
ArN_2^+Cl^- + C_6H_5CH = CHCHO \rightarrow C_6H_5CH = C - Ar - CHO
\]

Although α β - unsaturated acids such as cinnamic and maleic can be arylated by this method, decarboxylation usually accompanies arylation, the extent of decarboxylation depending upon the pH of the reaction mixture.

Borshe discovered that simple oximes could be similarly arylated, thus providing another route to the aromatic aldehydes and ketones from amines.
Beech has carried out these reactions using formaldoxime, acetaldoxime and acetaldehyde semicarbazone. Since nitrones are N-ethers of oximes and structurally similar to them, these reactions were carried out with 4, 5, 5-trimethyl-\(\Delta_1\)-pyrroline-1-oxide (XXIV). The experiments were done in sodium acetate buffers (pH 5-6) after the method described by Beech.

\[
\begin{align*}
\text{ArNH}_2 & \rightarrow \text{ArN}_2^+ \text{Cl}^- + \text{CHRNOH} \rightarrow R \cdot \text{Ar} \cdot C = \text{NOH} \rightarrow \text{ArCOR}
\end{align*}
\]

The p-chlorophenyl substituted nitrone (XXVIII) gave absorption peaks in the infra-red region as follows:

The C = C skeletal in plane vibrations appeared at 1600 cm\(^{-1}\) while the absorption at 1572 cm\(^{-1}\) in the unsubstituted nitrone has been shifted to 1540 cm\(^{-1}\) due to conjugation with the phenyl group. The CH out-of-plane deformation bands of the disubstituted benzene ring were also noticed in the region of 850 cm\(^{-1}\).

The ultraviolet spectrum of this compound exhibits bands at shorter wavelength 226 (\(\varepsilon 7500\)) and 232 (\(\varepsilon 7800\)) m\(\mu\), which could be
considered as the displaced and intensified local excitation band of benzene due to conjugation with the nitrone group. The long wavelength band at 298 m$\mu$ ($e$ 16,600) might be the electron transfer band in which the electrons of oxygen are transferred to the $\pi$-orbital of the aromatic ring.

The NMR spectrum of the compound (Fig. 2) also supports the structure of No. XXVIII. The resonance peaks at high field were the same as that of the parent nitrone. The deshielding of the protons of the aromatic nucleus ortho to the nitrone substitution is noticeable here as in the case of the carbonyl substituent. The two sets of interacting nuclei exhibit a spectrum of an $A_2B_2$ system. In this system, coupling between equivalent atoms plays a part in determining the nature of the spectrum. Out of the four coupling constants $J_{AB}$, $J_{AB}'$, $J_{AA}$, and $J_{BB}$, the spectrum depends upon the values of $J_{AA}$ and $J_{BB}$, also, because $J_{AB}$ is not equal to $J_{AB}'$. In the p-disubstituted phenyl group, with one substituent more electron withdrawing than the other, the A protons and B protons are respectively meta to themselves and ortho and para to one another. This makes the values of $J_{AA}$ and $J_{BB}$ approximately equal. Since the difference in chemical shift between the two sets of nuclei is large with respect to the coupling constant $J_{AA}$ or $J_{BB}$, the spectrum consists of four triplets which are symmetrical about the midpoint.

Further proof for the structure came from the preparation of the same compound using the corresponding Grignard reagent followed by further oxidation of the intermediate hydroxylamine.

p-nitrobenzene substitution in the nitrone was carried out by the
diazonium salt method. The p-nitrophenyl substituted nitrone XXIX shows absorption in the infrared region similar to the p-chloro compound. Additional peaks at 1520 and 1400 cm\(^{-1}\) are presumably due to C-NO\(_2\) stretching vibrations.

In the ultraviolet region the absorption peaks were shifted to longer wavelengths with higher intensity, 249 m\(\mu\) (11,400) and 348 m\(\mu\) (12,200) due to the additional conjugation with nitro-groups.

The NMR spectrum of this compound (Fig. 3) was very similar to that XXVIII. Since both the substituents of the p-di-substituted benzene nucleus were electron withdrawing in nature, the two sets of protons had comparable shielding. Therefore, the difference in chemical shift between them was small and this affected the spectrum by increasing the intensity of the inner-lines of the four triplets at the expense of the outer lines.

A pyridine ring was substituted in the \(\triangle^1\)-pyrroline-1-oxide by the same reaction. The 2-(\(\beta\)) pyridyl substituted nitrone XXX was a
hygroscopic base. The infrared spectrum of the freshly sublimed product
gave peaks at 1590 cm$^{-1}$ ($\text{C} = \text{N}$), 1550 cm$^{-1}$ (conjugated nitrone) and CH
deformation bands in the region of 700 cm$^{-1}$ and 1000 cm$^{-1}$.

![Chemical structure]

In the NMR spectrum of this compound, the low field regions are
from the four ring protons of the pyridine nucleus.

The signals at the lower field which overlap each other might be
due to the protons adjacent to the nitrogen of the pyridine ring. The
singlet at $\delta 8.5$ can be assigned to H-6' due to the absence of neighbour-
ing protons and this overlaps a broadened doublet, probably due to H-2'.
The broad signal centred at $\delta 1.4$ is most probably due to the H-4' proton
which interacts with neighbouring proton and also a little with protons
at C-2' and C-6'. The signal at $\delta 2.6$ is obviously due to the H-3' proton
as seen from its more complex splitting.

Substitution in the α-ketonitrone XXV was also carried out using
the p-chlorodiazonium salt. The peaks in the infrared region were at 740,
1543, 1600 and 1662 cm$^{-1}$ for this α- p-chlorophenyl substituted nitrone
XXXI. In the ultraviolet region the local excitation band of the benzene
nucleus was at 247 μ; the band at longer wavelength, 303 μ, which
could be due to the electron transfer band of the system was less intense
[ε 8210] than the corresponding band in the five membered ring [ε 16, 610]. This could be explained as due to some loss of coplanarity between the two rings, i.e. the probability of the transitions was lower than in the five membered ring. The NMR spectrum (Fig. 5) also supported this conclusion, for the ortho shielding effect of the nitrone group on the aromatic protons was not observed at all and there was only a single broad band for these protons.

In the case of the aromatic carbonyl compounds, it is known that the deshielding of the ortho protons is due to the anisotropic effect of the carbonyl group. This effect arises from the paramagnetic circulations induced by the components of the applied field in the plane of the trigonal carbon atom. Therefore, the deshielding effect of the protons will be greatest if they lie in the plane of the carbonyl group. The magnitude of the diamagnetic shift will be relatively small if the coplanarity is altered. If it is assumed that the α substituted p-chlorophenyl ring is not coplanar with the hydopyridine-1-oxide, then the ortho protons are removed from the expected deshielding area of the magnetically anisotropic nitrone and carbonyl groups.
The mechanism of these substitutions probably involves radical intermediates as seen from analogy with the Meerwein reaction.\textsuperscript{37} The phenyl radical is generated by the homopolar decomposition of the diazoacetate formed from the diazonium salt and sodium acetate.

\[
\text{C}_6\text{H}_5\text{N}_2 + \text{CH}_3\text{COO}^- \rightarrow \text{C}_6\text{H}_5\text{N} = \text{NOCOCCH}_3 \rightarrow \text{C}_6\text{H}_5^- + \text{N}_2 + \text{CH}_3\text{COO}^-
\]

The phenyl radical attacks the nitrone to give another nitrone radical

\[
\begin{align*}
\text{CH}_3 \quad \text{CH}_3 \\
\text{N}^+ \quad \text{N}^- \\
\text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5^- \\
\text{O} \quad \text{O}
\end{align*}
\]

The function of the cupric salt was probably to oxidise the radical and thus assist in the liberation of the proton.

\[
\begin{align*}
\text{CH}_3\text{COO}^- + \text{Cu}^+ & \rightarrow \text{CH}_3\text{COO}^- + \text{Cu}^{+ +} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{N}^- \quad \text{N}^+ \\
\text{C}_6\text{H}_5^- \quad \text{C}_6\text{H}_5 \\
\text{O} \quad \text{O}
\end{align*}
\]

The low yields obtained are similarly encountered in the Meerwein arylation reaction.\textsuperscript{40} This is not altogether surprising in view of the wide variety of reactions that diazonium salts undergo. The large amount
of tar could be due to diazo resins which are often associated with reactions of diazonium salts. Side reactions like the formation of azo compounds, replacement of the diazo group by halogen atoms, hydrolysis to phenol and deamination could also take place.

Despite the low yields these reactions seemed to be of importance in synthesis because more highly substituted heterocyclic compounds may be prepared by this method. The coupling of an aromatic ring to an aliphatic side chain can be achieved by the Grignard reaction but this suffers from some serious limitations. Arylmagnesium halides will react with other functional groups also and one cannot prepare Grignard reagents from aryl halides containing nitro-, cyano-, carbonyl and acyl groups among others. These groups, in contrast, activate the arylation by the diazonium salt method.

The large amount of tars and other side products produced in the arylation reaction suggested that it was principally radical mediated reaction. However, the possibility of a cation intermediate proposed by Meerwein cannot be discounted, since the back polarisability of nitrones can induce the formation of an aryl cation from the diazonium cation.
The α-ketonitrone XXV was found to undergo dimerisation on treatment with aqueous potassium chromate. The reaction was carried out to study the nature of the rearrangement of α-ketonitrones; aldonitrones in general are found to undergo rearrangement to their isomeric amides on treatment with reagents like acetic anhydride, sulphur dioxide, phosphorus pentachloride, and solutions of base in ethanol. Brady found the rearrangement to occur with the greatest ease on boiling N-methyl ethers of some aldoximes with acetic anhydride. Umezawa found sulphur dioxide and triphenyl phosphine also to be effective catalysts in the isomerization of nitrones. Kroehnke obtained a yield of 80 per cent of the rearranged product from the following aldo nitrone on treatment with acetic anhydride.

\[
\text{C}_6\text{H}_5\text{COCH} = \text{N-C}_6\text{H}_5 \rightarrow \text{C}_6\text{H}_5\text{COCONH}_2\text{C}_6\text{H}_5
\]

Though these reactions have been considered to be similar to the Beckmann rearrangement, Kroehnke found that they are not configurationally specific. In most cases the substituents do not migrate as in the case of classical Beckmann re-arrangement which implies that the mechanism operating here is different. He explained the rearrangement of aldonitrones to acid amides under "Beckmann condition" or in alkaline solution as occurring through a lactim intermediate as against the azennium ion intermediate in the classical Beckmann rearrangement. The Kroehnke explanation can be formulated as follows -
whereas Beckmann rearrangement is known to be as follows -

\[
\begin{align*}
R - C &= N - R' \\
\Rightarrow R - C &= N - R' + \text{H}_2\text{O}
\end{align*}
\]

Aromatic N-oxides also give similar results. With α- or γ-alkyl substituted N-oxides, side chain acylation occurs while in unsubstituted compounds, the reagents bring about a rearrangement to the 2-oxo compound.

In almost all mechanisms that have been considered for these reactions, the first step is protonation (or its equivalent) of the oxygen of the N-oxide by the reagent (i.e., with the equivalent of the acetylium ion of the acetic anhydride). The subsequent steps have been the subject
of much discussion, but the evidence as yet does not permit a clear choice between an ionic mechanism and one involving intermediate free radicals.

The rearrangement of the unsubstituted N-oxides to the oxocompounds was explained by Ochiai as an ionic mechanism involving a lactim intermediate as suggested by Kroehnke.

Bockelheide and Lehn who proposed both ionic and radical mechanisms, tried to distinguish between them by studying the rearrangement of some negatively substituted pyridine N-oxides; the ease with which 2-carboxypyridine N-oxide underwent dicarboxylation to give pyridine N-oxide and 2-pyridone led him to suggest that the reaction path was ionic.

The rearrangement of 2-picoline N-oxide to 2-acetoxyalkylpyridine was also studied by several groups of investigators. The elegant work of Traynelis and Marletto had supported the ionic mechanism, suggested by Patchen in his studies on the benzoylation of quinalidine N-oxide. The ionic mechanism was considered to proceed through an anhydride base (2) which probably resulted by abstraction of an acidic proton from the 2-methyl group (1) by acetate anion could rearrange to the product (3) either by an intra-molecular cyclic rearrangement or by a nucleophilic attack of acetate anion on the methylene carbon with elimination of acetate anion.
More recently Oae \(^{48}\) had studied the rearrangement of 2-picoline N-oxides using acetic anhydride with all the three oxygens equally enriched by \(^{18}O\). These results supported the above anhydrobase (2) and the conversion of this to 2-pyridinyl methyl acetate was best explained by intramolecular rearrangement though it is not easy to distinguish between ionic and radical intermediates for such a rearrangement.

Free radical mechanisms also appear plausible and Bockelheide and Harrington \(^{49}\) had proposed such a mechanism for the rearrangement of 2-picoline N-oxide with acetic anhydride.
Traynelis and Martello\textsuperscript{50} had also made some studies on the effects of radical inhibitors on these reactions. If the rupture of the $N \rightarrow O$ bond can be considered as a radical process, it would be reasonable to expect other amine oxides, including aliphatic tertiary amine oxides, to behave in the same way as 2-methylpyridine-N-oxide. This was found to be true. In the Polonovski reaction,\textsuperscript{51} tertiary amine oxides are found to undergo oxidative demethylation on treatment with acetic anhydride to give the $N$-acetylated secondary amine and formaldehyde.

\[
\begin{align*}
C_6H_5 - \overset{\text{CH}_3}{\underset{\text{CH}_3}{N \rightarrow O}} & \quad \rightarrow \quad C_6H_5 - \overset{\text{CH}_3}{\underset{\text{CH}_3}{N - \text{CH}_3}} \\
& \quad \rightarrow \quad C_6H_5 - \overset{\text{CH}_3}{\underset{\text{OCOCH}_3}{N - \text{CH}_3}} \\
& \quad \quad + \quad HCHO
\end{align*}
\]

Similarly, trimethylamine oxide and sulphur dioxide form a compound $\text{Me}_3\text{NOSO}_2$ which undergoes decomposition to dimethylamine, formaldehyde and sulphur dioxide.\textsuperscript{52} The catalysis of these reactions by some metal complexes lends support to the view that the reaction path may be radical-mediated. Amine oxides like $N, N$-dimethyltryptamine oxide undergo rearrangement in presence of $\text{Fe}^{3+}$ under mild conditions to give $N$-methyltryptamine and formaldehyde.\textsuperscript{53}

\[
\begin{align*}
\begin{array}{c}
\text{C}_{6}\text{H}_{5} - \overset{\text{CH}_3}{\underset{\text{CH}_3}{N \rightarrow O}}
\end{array}
& \quad \rightarrow \quad \begin{array}{c}
\text{C}_{6}\text{H}_{5} - \overset{\text{CH}_3}{\underset{\text{CH}_3}{N \rightarrow O}}
\end{array}
\quad \rightarrow \quad \begin{array}{c}
\text{C}_{6}\text{H}_{5} - \overset{\text{CH}_3}{\underset{\text{CH}_3}{N \rightarrow O}}
\end{array}
\quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
\text{HCHO}
\end{array}
\end{array}
\end{align*}
\]

The oxidative demethylation is effected via a metal chelate as
Other metal ions like Ru\(^{3+}\), Os\(^{3+}\), V\(^{4+}\) etc. which have the ability to co-ordinate in a higher oxidation state and provide the requisite binding sites for the oxygen of the N—O, can also be used as catalysts.

A similar reaction has been observed\(^{54}\) in the case of alkaloids like codeine-N-oxide which, on treatment with aqueous \(K_2\text{CrO}_4\) gives a base norcodeine. Bailey\(^{55}\) found \(K_2\text{CrO}_4\) to be a reagent for the fission of tertiary amine oxides in general and used it to prepare pseudobrucine from brucine-N-oxide.
Since α-ketonitrones were expected to behave similarly, the 5,5-dimethyl-α-ketonitrone XXV was boiled with aqueous \( \text{K}_2\text{Cr}_2\text{O}_7 \) for two hours. The product XXXII obtained had a high melting point (264°) and the following spectroscopic characteristics:

- \( \nu_{\text{max}} \approx 3300 \text{ cm}^{-1} \) (very weak), 1660, 1700, 1558 and 1540 cm\(^{-1}\)
- \( \lambda_{\text{max}} \approx 275 \text{ m\(\mu\)} (\varepsilon = 22,500) \)

The absorption peaks at 1540 and 1558 cm\(^{-1}\) suggested the existence of a dinitrone system, but the possibility of an amide II band had also to be considered. The peak at 3300 cm\(^{-1}\) was very weak and not affected by deuteration in CF\(_3\)COOD, suggesting the absence of -OH or NH; this was
confirmed by the failure of methylation and acetylation reactions. The carbonyl bands at 1660 and 1700 cm\(^{-1}\) were quite strong. Reduction of the product with KBH\(_4\) gave a compound XXXIII - C\(_{14}\)H\(_{28}\)O\(_4\)N\(_2\) whose infra-red spectrum showed the disappearance of both carbonyl bands and the appearance of a strong hydroxyl band at 3300 cm\(^{-1}\). This suggested that amide groups were not likely to have been present in the original molecule, since they are not normally reduced by KBH\(_4\). The reduction product readily reduced triphenyltetrazolium chloride in alkaline solution to the red formazan, a reaction characteristic of hydroxylamines.\(^{56}\) Reduction of nitrones to hydroxylamines by hydrides is well known. Since the nitrogen in the nitrones is at a high oxidation level, further reduction to secondary amines is possible,\(^{31}\) and catalytic hydrogenation of the reduced product was carried out using pre-reduced platinum oxide as catalyst. The base was isolated as its hydrochloride C\(_{14}\)H\(_{28}\)N\(_2\)O\(_2\)\_2HCl XXXIV. The absorption peaks in the infra-red region were as follows - 1600 cm\(^{-1}\), 2485 (\(\nu\)), 2700 (\(\nu\)), 3280 cm\(^{-1}\). The band at 3280 cm\(^{-1}\) could be due to OH or NH, while those at 2700 and 2485 cm\(^{-1}\) could be due to -NH\(_2\). The peak at 1600 cm\(^{-1}\) was shown to be an NH deformation band, as its intensity was markedly reduced on deuteration.
Electrometric titration of the hydrochloride XXXIV disclosed two groups of different basicity. The difference between the two pKa values was 2.75. Δ pKa values of some other di basic system (57,32) could be useful to compare with the present system.

\[
\begin{align*}
\text{C}_{14} \text{H}_{28} \text{N}_{2} \text{O}_{2} \cdot 2 \text{Hd} & \quad \text{pK}_a_1 \ 5.65 \quad \text{pK}_a_2 \ 8.4 \quad \Delta = 2.75 \\
+ \quad \text{NH}_3 - \text{CH}_2 - \text{CH}_2 - \text{NH}_3 & \quad 7.00 \quad 10.09 \quad 3.09 \\
+ \quad \text{NH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{NH}_3 & \quad 8.64 \quad 10.62 \quad 1.98
\end{align*}
\]

Two carbonyl groups with a dinitrone system suggested that the compound was a dimer. Assuming the mechanism of dimerisation to be ionic in nature, possible structures would be 2-2', 2-4' and 2-6' dimers. This is based on the known nucleophilic reactivity of the α-ketonitrone XXV as shown by the D-exchange reactions (Table I). The electrophilic centre would certainly be expected to be the 2-position.
pKa values can be correlated with spatial proximity of the nitrogens and the value obtained in the electrometric titrations of the hydrochloride XXXIV, though lower than obtained in the case of other dibasic systems, suggested the presence of an α-dinitrone system in the starting material. The structure would be therefore either a 2-2' or 2-6' dimer.

The compound was not sufficiently soluble in any ordinary neutral solvents to give reasonably concentrated solutions for carrying out most reactions that might help to elucidate its structure. The compound did not give satisfactory reactions of carbonyl compounds, e.g., no dinitrophenylhydrazone was formed. This is not unexpected, probably if a 2-2' linkage exists.

1,2 glycol splitting reagents like sodium metaperiodate have been successfully used to distinguish between 2,2' and 2,3' bipyrrrolidinyl systems. Oxidative degradation of the corresponding bishydroxylamines resulted in an α-dinitrone system in the case of 2,2' linkage, while in the case of 2,3' system oxidation proceeded beyond the dinitrone stage ending in degradative products.
From solvent CDCl₃

From solvent CF₃COOH

FIGURE 6
When the bis-hydroxylamine XXXIII of the present system was reacted with NaIO₄, the product was a light yellow viscous oil of which no crystalline derivatives could be prepared. The absorption peaks in the infra-red region were 3450 cm⁻¹ (broad), 1740 cm⁻¹, 1670 cm⁻¹ and 1580 cm⁻¹ (weak). The strong hydroxyl band was found to be due to the hygroscopic nature of the compound because the intensity of the band was found to be less with the freshly distilled product. The band at 1580 cm⁻¹ indicated that the product formed could contain a pyrroline oxide. Its formation could be explained as follows -

Copper catalysed aerial oxidation of the hydroxylamine XXXIII which might have given a dinitrone afforded only intractable products.

Either the formation of a copper complex or the oxidative cleavage of the rings might have resulted in a mixture of compounds. Similarity of the infra-red spectrum of this product with the periodate reaction product supports the latter possibility. The products were sticky mixtures in both cases and could not be separated by chromatography or crystallization.

Comparison of the NMR spectra of both the monomer and the dimer in trifluoroacetic acid confirmed that the linkage was 2,2' since no
CHEMICAL SHIFT VALUES AND EXCHANGE BEHAVIOUR
OF PROTONS OF THE NITRONE XXV AND ITS DIMER.

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>SOLVENT</th>
<th>CHEMICAL SHIFT OF PROTONS AT; (τ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C - 2</td>
</tr>
<tr>
<td>MONOMER</td>
<td>CDCl₃</td>
<td>+ 2.91</td>
</tr>
<tr>
<td>MONOMER</td>
<td>CF₃COOH</td>
<td>+ 2.30</td>
</tr>
<tr>
<td>DIMER</td>
<td>CF₃COOH</td>
<td></td>
</tr>
</tbody>
</table>

All signals were sharp except where noted.

• Exchange observed in Et₃N.

† An exchanged (Et₃N) sample did not back exchange in this solvent.

○ Exchange occurred at this position slowly on standing in 80% CF₃COOD + 20% D₂O for 48 hr.

= J₂,₆ = 0.9 c/s. The value J₂,₆ = 1.1 as quoted by Sternhell, is for D₂O solution.
signal was observed for the 2-protons. The large downfield shift of the C-2 proton of the monomer in CF₃COOH together with smaller shifts at C-4 and C-6 in both the monomer and dimer suggests that these compounds are completely protonated at the oxygen of the nitrone group in this solvent (Fig. 6). The simplicity of the spectrum reveals the structure of the dimer as highly symmetrical and the closely parallel chemical shifts with loss of vinyl proton in the dimer is most readily explained in terms of the 2,2' structure.

Further proof was obtained from the behaviour of the dimer on deuterium exchange [Table 2], using both acidic and basic catalysts. The dimer exchanges hydrogen very well in pyridine/D₂O with triethylamine as catalyst. Exchange took place at both 4,4' and 6,6' methylene protons as in the monomer, the rates of exchange following the same pattern as in the monomer, i.e., the 4,4' position exchanged faster than the 6,6'. The deuterated compound was found to be stable, in its acid back exchange did not take place when the spectrum was taken in pure CF₃COOH. However, the exchange of H was found to take place in CF₃COOD containing 20 per cent D₂O, but was confined to the 4 position in both monomer and dimer. The reaction sequence probably depends upon the presence of the D₂O required as a base. Thus -
FIGURE 7.
Moreover, the NMR spectra of the bishydroxylamine XXXIII in DMSO and the diolhydrochloride XXXIV in D$_2$O were very similar to those of the corresponding monomeric derivatives (Fig. 7).

The ultraviolet spectrum of the dimer XXXII also showed very little difference from that of the monomer. Monomer XXV - 280 mµ (17,500); Dimer XXXII 275 mµ (22,500). The increase in the intensity of absorption was also less than expected. This could be attributed to the nonconjugation between the groups since the two tetrahydro rings must be forced out of coplanarity by the four oxygen atoms disposed about the 2,2' band.

Mechanism of dimerisation

$\Delta^4$-pyrroline-N-oxides, although not usually subject to spontaneous dimerisation, were found to undergo base catalysed dimerisation and addition reactions which gave nitroone-hydroxylamines analogous to aldolic dimers
in the carbonyl series. Such aldol type dimerisation was effected by the use of powerful ether soluble base catalysts such as triphenylmethyl sodium. However, the use of sodamide in liquid ammonia gave another dimer in a reaction analogous to the benzoin reaction of benzaldehyde, specifically catalysed by CN⁻. Formation and stabilisation of the intermediate carbonion was described as follows.

\[
\begin{align*}
\text{CH}_3\begin{array}{c}
\text{H}\
\text{N}\
\text{O}^-
\end{array} & + \text{Base} \rightarrow \begin{array}{c}
\text{N}\
\text{O}^-
\end{array} \leftrightarrow \begin{array}{c}
\text{N}\
\text{O}^-
\end{array}
\end{align*}
\]

In the biological action of thiamine, a heterocyclic anion of similar type was found to be an important reaction intermediate. The anion formed from these thiazolium salts are found to be stabilised by resonance contributions from neutral carbene structure as in the above case.

\[
\begin{align*}
\begin{array}{c}
\text{R}'\
\text{S}\
\text{N}\
\text{R}
\end{array} & \leftrightarrow \begin{array}{c}
\text{R}'\
\text{S}\
\text{N}\
\text{R}
\end{array}
\end{align*}
\]

Kroehnke and coworkers have proved that the condensation of certain pyridinium compounds with aldehydes occurs through anions of type given below.
Formation of such a reactive heterocyclic anion thus seems to be a plausible intermediate stage in the present system. The reaction might be presumed to follow either of two pathways, addition of an anion to another molecule, which then oxidises and rearranges to a dimer (A), or oxidation of the anion to a radical which then dimerises (B).

The available evidence does not permit a clear choice between these two possibilities. Formation of the same dimer in very low yield when the nitrone was treated with $K_3 Fe(CN)_6$ in sodium bicarbonate
solution however, lends some support to the anion oxidation mechanism. The anion formation and stabilisation could be explained by the following resonance structures -

The isomeric α-ketonitrone XXVI did not follow these reaction pathways supporting the above line of reasoning. Any mechanism involving a free radical intermediate was ruled out as the reaction was not induced by initiators like Fremy's salt. Moreover the reaction was not spontaneous but slow and steady.

The unsubstituted α-ketonitrone \(^6\) (5,6 dihydro-3-(4H) pyridone-1-oxide) also fails to dimerise. Presumably the nitrone XXV inhibits side reactions involving the 4 and 6 positions so that the compound and its anion stay in solution long enough to dimerise in good yield, whereas the unsubstituted compound does not.
ACID CATALYSED ACYLATION OF THE α-KETONITRONE XXV AND ITS REARRANGEMENTS

Acid catalysed acylation of the α-ketonitrone XXV with acetic anhydride:

In an attempt to find a suitable reagent for isomerisation of the α-ketonitrones, the ketonitrone XXV was treated with acetic anhydride in the presence of an acid catalyst. The desired rearrangement of the nitrone to the isomeric amide evidently occurred as shown by the appearance of a sharp infra-red band at 3320 cm⁻¹; but acylation of the ketone at 3 position of the nitrone apparently took place simultaneously. The product was a crystalline compound C₁₁H₁₃NO₃ (colourless needles, m.p. 156°). Although absorption in the infra-red region, 3320, 1763, 1688, 1650, and 1610 cm⁻¹, suggested the presence of a vinyl ester group, the compound was stable to acid hydrolysis indicating that the product was not an enol ester.

Acetylation of a ketone having α-hydrogen atoms can result in α-acylation (1) or in O-acylation of the enolic form (2). The resulting enol ester can be further acylated at the α-carbon atom as in (3). An acid catalysed acylation furnishing meta-dioxenones has been reported recently and appears to have resulted in the formation of a gem-diacetate and subsequent cyclization (4).
Characterisation of the acylated nitrone

Three structures XXXV, XXXV-a, XXXV-b are conceivable for the acylation product from the ketonitrone XXV in the light of spectroscopic, analytical and chemical evidence. XXV could arise from cyclization of (1) while XXXV-a and XXXV-b could result from cyclization of (3). The ultraviolet absorption of this white compound 323, 277 and 238 m\(\mu\) was similar to that of \(\alpha\)-pyrones (300 m\(\mu\))\(^{64}\) while the infra-red spectrum was similar to that of the vinyl ester of an \(\alpha, \beta\)-unsaturated acid.\(^{65}\) An \(\alpha\)-pyrone structure XXXV or XXXV-a can therefore be considered for this compound. The absorption of \(\gamma\)-pyrones in both ultraviolet (275 m\(\mu\))\(^{66}\) and infra-red regions \(^{67}\) (\(\nu = 0\) at 1650 cm\(^{-1}\)) are similar to those shown by hexadienones and compare less favourably with those of the white compound. The NMR spectrum of this compound (Fig. 8) supported the structure XXXV.
The doublet at 6 6.7 is ascribed to the methylene protons adjacent to the amide nitrogen, since on deuteration this signal collapses to a broadened singlet. Therefore the coupling was with the NH proton of the amide group. In compounds of this type where proton exchange is not pronounced such coupling of a protons with the amide proton is found to occur and can be measured. The similarity of the spectral properties of XXXV and XXXVI was further evidence in support of structure XXXV.

The mass spectrum was likewise consistent with this structure and is discussed in detail in the next section.

Catalytic hydrogenation of the compound XXXV (Adam's catalyst in EtOH at RT) furnished a compound C_{11}H_{15}NO_3 (colourless prisms, m.p. 184°).

υ_{max} 3300, 1743, 1658 and 1603 cm^{-1}; λ_{max} 278, 230 μ. The uptake of one mole of hydrogen and the NMR spectrum of the dihydrocompound (Fig. 9) gave evidence for the structure XXXVII, evidently the product of 1,2 addition.
This was somewhat unexpected as α-pyrone behaves as dienes giving 1,4 addition products. This could be due to direct steric hindrance to 1,4 addition by the methyl groups. Alternatively, if addition of the first H is assumed to take place at the carbon atom adjacent to C = O in the pyrone ring, the subsequent alteration in conformation may well result in lifting the molecule off the catalyst surface, with the result that 1,4 addition can no longer occur. The presence of the gem-dimethyl group at position may also be the reason for the change in the conformation after the hydrogenation of the first double bond.

**Action of base on the compound XXXV**

Although attempts to hydrolyse this compound with acid were unsuccessful, alkali was effective and a yellow coloured solution resulted, as would be expected from the hydrolytic cleavage of an α-pyrone ring. Mild alkaline hydrolysis of α-pyrone usually results in a yellow solution of the salt of the corresponding ketonic acid. Although acidification at this stage can regenerate the original pyrone, more drastic alkaline hydrolysis can induce reverse aldol condensation to degrade the molecule to carboxylic acids.
The same crystalline compound $C_{10}H_{15}NO_2$ (long yellow needles, m.p. $130^\circ$) was isolated from this reaction of base on the compound $XXXV$ either before or after acidification. Absorption in the infra-red region ($3250, 1705, 1635$ and $1583$ cm$^{-1}$) however, showed that the compound was not a carboxylic acid (as was also indicated by its extraction from alkaline solution) and suggested the presence of a ketone; the absorption maximum in the near visible region ($382$ m$\mu$) of the ultraviolet showed the presence of a highly conjugated system. The NMR spectrum of this yellow compound (Fig. 10) was similar to the compound $XXXV$ in having the gem dimethyl group resonance peak at $\tau 8.90$, and a split methylene at $\tau 6.74$. The peak for NH proton appeared at $\tau 0.44$. The split methylene was found to collapse to a singlet on dueteration in this case also. In addition to the methyl proton attached to an electron attracting group at $\tau 7.83$, a peak for methylene protons at $\tau 7.53$ and one of the olifinic proton $\tau 4.17$ were also present.

**Characterisation of the above yellow compound.** Catalytic hydrogenation resulted initially in the absorption of hydrogen as evidenced by the loss of colour but the product was unstable and reverted to the starting material.
on attempted work up. However NaBH₄ reduction gave a stable product (crystalline colourless plates m.p. 140°C) which, due to its high solubility in aqueous solution, could not be isolated in sufficient quantity for full characterisation. Infra-red absorption at 3400 and 1635 cm⁻¹ showed that reduction of only one of the carbonyl groups had occurred (presumably a ketone). The NMR spectrum of this compound in D₂O or DMSO showed absorption only in the high field region indicating the absence of the vinyl proton. The split methyl group adjacent to the gem-dimethyl followed by a multiplet suggested that reduction of a double bond as well as a carbonyl group had taken place.

Thus the chemical and spectroscopic evidence indicate the presence of a methyl ketone and a double bond in the yellow compound. The absorption in the UV region 382 µm suffers a hypsochromic shift in alkaline medium while there is no appreciable change in acidic medium confirming the absence of a basic nitrogen (cf. structure (b) below).

Spectroscopic evidence allows a choice between several structures as follows; but at this stage no structure to fit all the available evidence could be assigned. The major difficulty was the apparent absence of allylic coupling in the NMR which would be expected in all structures except (b), while (a) was consistent with hydrolysis and decarboxylation of the α-pyrone ring, was also not in agreement with the NMR.
Surprisingly the same yellow compound was obtained when the nitrone was reacted with isopropeneyl acetate in presence of catalytic amount of p-toluenesulphonyl chloride. The reaction was carried out to investigate the formation of the white compound XXXV, as it was felt that an enol acetate might be involved as an intermediate. Evidently the reagent had brought about the $N \rightarrow C$ migration of the oxygen of the N-oxide, but it appeared possible that incorporation of acetone might also have occurred in this reaction. Treatment of the nitrone with acetone and acetic anhydride under the same experimental conditions again gave the same compound and the participation of acetone was confirmed by substitution of D$_6$ acetone in the reaction mixture. The product which was otherwise indistinguishable from that obtained from ordinary acetone, failed to show the methyl signal at $\tau 7.83$ in the NMR spectrum, but all the other signals were present.

As the products of the reaction of nitrone with isopropeneyl acetate and acetone are the same and the deuterium labelling process has indicated that the methyl group arises from acetone, it appears that the simplest explanation would involve condensation of acetone at the 3 carbonyl of the $\alpha$-ketonitrone XXV. While structures (c) and (d) can be considered for the yellow compound in the event of such a condensation, structure (c) seems to be the more likely one as base or acid catalysed aldol condensation followed by dehydration to give $\alpha$, $\beta$ unsaturated ketones are well known synthetic sequence. On the other hand structure (b) would involve attack of acetone on the electrophilic 2-position of the nitrone to give a substituted hydroxylamine whose dehydration under the specified condition could not expect to take place.
As a final check to ensure that deuterium labelling obtained in the D₆ acetone reaction was not merely due to deuterium exchange, the yellow compound, (the structure of which will be assumed to be XXXVIII) was submitted to the action of D₂O and base.

Exchange occurred at positions 1', 3' and 4' as well as the NH when the compound was refluxed with a strong base (Triethylamine), EtOD and D₂O. Comparative rate of exchange was observed by NMR in CDCl₃, D₂O and NaOD. The rate of exchange at position 4' was faster than at either 1' or 3' and the olefinic proton at 1', in turn exchanged faster than methyl protons at 3'. The rate was nearly as fast as the methylene proton. Partial back exchange of the olefinic proton only was observed on treatment of the fully deuterated material with water in the absence of base - a rather unexpected result, i.e. the rate at position 4' is greater than at 1' in base but less in the absence of base. Exchange at the methylene proton at 4' position alone could be achieved by the action of D₂O in presence of a weak base (K₂CO₃, 0.4 mole).

Mass spectra of the yellow compound XXXVIII C₁₆H₁₅NO₂, its 3'-d₃ derivative C₁₆H₁₅DNO₂ and its 4'-d₃-derivative C₁₆H₁₅DNO₂ were measured. The mass spectrum of the yellow compound exhibited a fragmentation path similar to that of a methyl ketone. A comparative study of the spectra of deuterated compounds with the undeuterated one gave some valuable information.
These results made it clear that in D\textsubscript{3} compound incorporation of deuterium had taken place at the methyl group of a methyl ketone while the D\textsubscript{2} compound had no deuterium at the methyl ketone. (Full details are given in the next section). Thus it is not possible for the product from D\textsubscript{6} acetone to have arisen merely by exchange, tending to confirm the original theory of condensation of acetone at the 3-carbonyl group of the \( \alpha \)-ketonitrone XXV.

**Reaction of the nitrone XXV with methyl acetoacetate**

As the same product was obtained from the acid catalysed reaction of the nitrone with either isopropenyl acetate or with acetone and acetic anhydride, it was reasonable to conclude that the reaction was essentially a keto-methylene condensation at the 3-position of the \( \alpha \)-ketonitrone XXV. If so, it would be expected that similar condensation could occur with any system capable of forming the essential enol intermediates. The reaction of the nitrone with methyl acetoacitrate was therefore carried out. This reaction yielded two compounds. One of them was a light yellow crystalline compound \( \text{C}_{10} \text{H}_{15} \text{NO}_3 \) - XXXIX (small needles, m.p. 98\textdegree). Spectroscopic characteristics of this compound was similar to those of the yellow compound XXXVIII \( \nu_{\text{max}} 3330, 1718, 1640 \) and 1623 cm\(^{-1} \); \( \lambda_{\text{max}} 368 \text{ m}\mu \). In the NMR spectrum (Fig. 11) however, the position of the resonance peak of the methyl protons in this compound (\( \gamma 6.3 \)) was downfield compared to that in the compound XXXVIII (\( \gamma 7.83 \)). The greater deshielding of the methyl resonance in the compound XXXIX could be attributed to the presence of an extra electronegative oxygen adjacent to the methyl group, i.e. a methoxy carbonyl group. Chemical analysis and other spectroscopic evidence supported the presence of an ester group in the compound XXXIX, the mass
spectrum likewise showed fragmentation pathways which were analogous to those of the yellow compound XXXVIII as well as confirming the presence of a methyl ester group [(M-15)$^+$, (M-31)$^+$, (M-59)$^+$]. The striking similarity of these two compounds XXXVIII and XXXIX in all their spectroscopic properties suggests that the compound XXXIX is an $\alpha,\beta$-unsaturated ester.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH} & \quad \text{CH}_3 \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Although condensation of the $\beta$-ketoester, similar to acetone at the 3-position of the nitrone XXV is expected to be the first step, the final product XXXIX obtained must have been the result of loss of the acyl group from the intermediate substituted $\beta$-keto ester.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH} & \quad \text{CH}_3 \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

It is interesting to note in this connection that the second product obtained from the reaction of the nitrone XXV with methyl acetoacetate is the same compound XXXV first obtained from the keto nitrone XXV by acetic anhydride and the significance of this will be discussed later.

**Oxidation of the yellow compounds XXXVIII and XXXIX**

The structural similarity of these two compounds was also revealed.
by their oxidation with neutral KMnO₄ at room temperature, which gave the same compound \( \text{C}_7\text{H}_1\text{NO}_2 \) (colourless feathery crystals, m.p. 106°). Absorption peaks in the infra-red region 3300, 1740, 1698 cm⁻¹ as well as in the ultraviolet (255 mµ) indicated the presence of \( \alpha \)-diketone system. The NMR spectrum of this compound (Fig. 12) was as follows.

The fragmentation path in the mass spectrometry (next section) together with the NMR spectrum was in accord with structure XXXX.
MASS SPECTRA

The structure of an organic compound can be elucidated with the help of mass spectrometry by following changes in the fragmentation pathways on isotopic substitution. The structure of the yellow compound XXXVIII was studied in this way; the labelling was carried out at the methyl and methylene protons separately. A mild base catalysed exchange reaction of the yellow compound XXXVIII exchanged the methylene protons at the γ-position of the α, β-unsaturated ketone XXXVIII-D₂. Although base catalysed exchange was found to occur in other positions of the molecule also (page 48), preferential exchange at the 4-position was effected by using mild base catalyst (K₂CO₃, 0.04 mole). The reaction was followed by NMR and arrested by acidification immediately after the exchange at 4-position was complete. This deuteration was found to accompany with partial deuteration also (of only one H atom) as seen from the mass spectra. Synthesis of the yellow compound XXXVIII from the nitrone using D₆-acetone gave the methyl-deuterated compound C₁₀H₁₂D₂NO₂ (page 47). The vinyl proton was found to be free from deuterium by NMR. As the fully deuterated sample (using (C₂H₅)₃N catalyst) showed that the vinyl proton could exchange back very easily (page 48) such a back exchange might have taken place in the D₆-acetone reaction, probably during the process of the isolation of the deuterated compound. Thus the absence of D at this position has no real significance.

\[ \text{XXXVIII} \]
\[ \text{XXXVIII-d₃} \]
\[ \text{XXXVIII-d₂} \]
\[ \text{XXXIX} \]
A comparative study of the mass spectra of XXXVIII, XXXVIII-d₂, XXXVIII-d₃ along with the ester XXXIX (which has a similar structure) has been carried out. The ion corresponding to m/e 181⁺ in the spectrum of the compound XXXVIII is the molecular ion. The shifting of this peak to mass 183 and 184 in Fig. 14 and 15 is in accordance with its deuteriation to XXXVIII-d₂ and XXXVIII-d₃. The peak at mass 166⁺ in the yellow compound XXXVIII indicated a loss of 15⁺; a peak appeared at the same mass in the d₃ species (loss of 18) while in the d₂ species the peak was at 168⁺ (M-15). The mass loss was thus due to CH₃ and not NH and the change to M-18 in the d₃ species showed that deuterium substitution was at the lost methyl group. There are three methyl groups in the molecule, but the method of synthesis and the NMR spectrum of the d₃ species (previous section) rule out the presence of the isotope in the gem-dimethyl group. Hence the fragmentation of the molecule would be

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{C} = \text{O} \\
\text{O} & \quad \text{C} = \text{O} \\
\text{N} & \quad \text{C} = \text{O}
\end{align*}
\]

\[+^{+} \quad -15\]

The cleavage of c-c band adjacent to a carbonyl group with the retention of the charge on the oxygen containing fragment as proposed here is very common. Meta stable peaks were observed for this process. Loss of 15 occurred also in the ester XXXIX from the molecular ion peak 197⁺. This compound gave another peak at 166⁺ (M-31) which could be ascribed to fragmentation of the methoxyl group.
The peak at mass 138 appeared in all three spectra (XXXVIII, XXXVIII 3 and XXXIX), a corresponding peak at m/e 140+ in the d2 species, showed that the deuterium of the d2 species was not lost in this fragmentation.

The metastable peak (m 105, 3) in Fig. 13 indicates that the peak at 138+ arises by a loss of 43 from the molecular ion; a number of mechanisms can be formulated for this loss from 181+.

Mechanism (2) proposes the heterolysis of a C-N bond and expulsion of a neutral entity NH = C = O to give the cyclobutane ring XXXVIII - d.
The mechanism (3) involves the loss of the gem-dimethyl group after a hydrogen transfer reaction, initiated by cleavage α- to the nitrogen has the additional advantage that the cleavage yields an allylic radical.

Discrimination between these mechanisms is possible by comparison of the mass spectra of the deuterated compounds. In the XXXVIII-d₃ species, the peak at mass 138 (M-43) does not shift, indicating that the fragment lost must contain all the deuterium atoms; i.e., it must have been the group -COCO₃ as indicated by mechanism (1). Confirmation was seen in the spectrum of the XXXVIII - d₂ compound, where the fragment lost was 43 (i.e., no deuterium was lost); the occurrence of the same peak in the ester XXXIX (at mass 138 in this case M-59) is consistent with this interpretation.

Not all the ion current for mass 138, however, was due to mechanism (1), as shown by a peak at m/e 141⁺ in the spectrum of the XXXVIII - d₃ species. Thus there was evidently a different fragment of mass 43 (not containing the CO₃ group) lost from this molecule. A corresponding loss of 43 was also found in the ester XXXIX (197⁺ — 154⁺ + 43 ). Such a loss in either XXXVIII or XXXVIII - d₂ would be indistinguishable from the alternative loss of 43 associated with the acetyl group, but the intensity of the 138⁺ peaks in these compounds were such as to suggest that they include fragments from all modes of fission.

The ion at mass 84 in the spectrum of XXXVIII was seen to originate by loss of 54 from the ion 138⁺ (m/z 138+ + 54) → 84⁺. The deuteration shifts (to 87⁺ in XXXVIII - d₃, unchanged in XXXVIII - d₂ ) clearly showed (1) that the acetyl group was not lost and (2) that the methylene group at the 4...
position formed part of the fragment lost. The fragmentation pathway of this ion thus be summarised as \( 181^+ \rightarrow 138^+ \rightarrow 84^+ \). The loss of 54 from 138\(^+\) could be an extension from either mechanism (2) or (3). The fragmentation using the mechanism (2) has been depicted in the sequence XXXVIII\(-d\) to XXXVIII\(-dd'\). The cyclobutane structure of XXXVIII\(-d\) probably facilitates hydrogen rearrangements as described below. This rearrangement could possibly lead to a fragmentation (XXXVIII\(-dc'\)).
However, the loss of NHCO according to the mechanism (2) which involves formation of a symmetrical ring would demand loss 54 as well as 56 in the XXXVIII-\(\text{d}_2\) species. The absence of a peak at 86\(^+\) in the mass spectrum of the \(\text{d}_2\) species clearly indicates that this formulation is not correct. Alternatively the application of mechanism (3) leads, through the \(\Delta\) \(1,6\) pyrroline structure XXXVIII-\(e\) with a hydrogen (or deuterium) rearrangement to the six-membered structure XXXVIII \(eb'\). This rearrangement permits rationalisation of the loss of 54 to include the deuterium atoms originally present in the XXXVIII-\(\text{d}_2\). The intermediacy of a structure such as XXXVIII-\(e\) is, of course, not mandatory, (i.e. a six-membered structure could have resulted by a more direct process).
The peak at m/e 97\(^{+}\) appeared in the spectra of both XXXVIII and XXXVIII-\(d_2\) but was shifted to mass 100 in the \(d_3\)-species. This again indicated that the ion corresponding to this peak arose by the loss of a fragment containing the methylene group at the 4-position of XXXVIII but not the acetyl group. Although there was no metastable peak indicating the origin of this ion at 97\(^{+}\) (100\(^{+}\) in the \(d_3\)-species), it could be either from the molecular ion 181\(^{+}\) (184\(^{+}\) in the \(d_3\)) or from the ion at mass 138 (141 in the \(d_3\)) as both still retain their acetyl group. Loss of 84 (86 in the \(d_2\)) from the molecular ion could be formulated as follows:

\[
\begin{align*}
\text{m/e 181} & \quad \rightarrow \quad \text{m/e 97} \\
\text{CH}_2=\text{N} & \quad + \quad \text{CH}_3\text{C}=\text{C}D_2
\end{align*}
\]

The peaks at 70\(^{+}\) and 55\(^{+}\) were common to all spectra and thus did not involve either of the deuterated sites. Their relationship is shown by a metastable peak at m\(^{\star}\) 43.21 corresponding to 70\(^{+}\) \(\rightarrow\) 55\(^{+}\). Presumably \(\text{(a)}\) there is a m\(^{\star}\) for 70\(^{+}\) from 184\(^{+}\) in XXXVIII-\(d_3\) compound.
these ions have their origin in the nitrogen containing part of the molecule as shown below and could be rationalised along the following lines -

The loss of 28 from the molecular ion, in all spectra except that of XXXVIII, revealed by a metastable peak could be that of the carbonyl group at the 2-position, arising from α-cleavages. The loss of 15 from this ion 153+ could be either one of the methyl groups of the gem dimethyl or the NH since the loss is common to all spectra. It is difficult to distinguish between these two without proper deuteration experiments. Deuteration at the nitrogen would help to understand this loss of 15 as well as that of 35 (OD₂OH) outlined below. Labelling at the 6 position could also help to confirm the nature of hydrogen rearrangements postulated in earlier fragmentation schemes.

Finally the peak at mass 149 in the d₃ species can only be logically interpreted as loss of OD₂OH; it is puzzling that loss of CH₂OH is not observed in the other two compounds (XXXVIII and XXXVIII-d₂). There does
not seem to be any reasonable explanation for this difference unless it is to be ascribed to an isotope effect - a most unsatisfactory theory. The loss of CD$_3$OH could be rationalised as

Mass spectra of the oxidation product XXXX

The peak at mass 141$^+$ in the mass spectra of the compound XXXX corresponds to the molecular ion. The metastable peak at 112.7 indicates that the base peak at 126$^+$ arises from this molecular ion by loss of 15. The cleavage of a methyl group from the gem-dimethyl could lead to an ion 126$^+$ which has a high resonance stabilisation with an aromatic structure (XXXX-a). Loss of a carbonyl from XXXX-a, through the intermediate structure XXXXb group would give rise to an ion m/e 98$^+$ (XXXX-c supported by the metastable peak at m$^*$ 76.3). The next peak in the spectrum is at mass 83$^+$ whose origin from the ion m/e 126$^+$ (XXXX-a) is indicated by the metastable peak at mass 54.7. The mode of formation of this ion (XXXX-d) by loss of 43 could be described as the fission of a neutral entity NHCOO from XXXX-a through the ion XXXX-b.

The metastable peak at 30.9 indicates the fragmentation pathway of XXXX-c at mass 98$^+$ to an ion at mass 55$^+$ which could be depicted as XXXX-e by another loss of 43. This is probably the same group NHCO lost through a different pathway.
The loss of 18 from 126\(^+\) could be due to H\(_2\)O (126\(^+\) → 108\(^+,\) \(m/\ell\)); with an enolizable diketone system this fragmentation is not altogether surprising and can be formulated as XXXX-f. The metastable peak at 85\(^*\) indicates an alternate pathway for 98\(^+\) \([113^+ (\text{XXX}-g) \rightarrow 98^+]\). The ion XXXX-g probably arises from the molecular ion by a loss of 28 (C = 0). The peak at 41 is probably due to a loss of 42 (CH\(_2\) = C = 0) from 83\(^+\) as shown in XXXX-h.

In summary, the fragmentation of the oxidation product was relatively simple and consistent with the structure assigned.
Mass spectrum of the acylated product XXXV

The peak at mass 207 in the spectrum of this compound (Fig. 18) corresponds to the molecular ion; the next peak is at 206$^+$. 207$^+$$\rightarrow$$ 206^+ (m/z 205) which appears to be a favourable process can be visualised as shown in XXXV (a) $$\rightarrow$$ XXXV (b); a mode of fragmentation unique to this compound whose structure differs from that of the compound XXXVIII only in the position and type of substitution. However the existence of an aromatic α-pyrone ring evidently controls the breakdown of the ion. Thus in the compound XXXVIII cleavage results in the loss of the substituents (e.g. = CHCOCH$_3$) but in XXXV the nitrogen-containing ring itself is to be regarded as a substituent (of the α-pyrone ring), and fragments until some degree of aromatic stabilisation has been attained. The removal of a methyl peak following this H-loss to give the ion XXXV-c is quite understandable as it leads to a stable conjugated system. This loss of 15 (206$^+$$\rightarrow$$ 191^+$) is supported by a metastable peak at $m^* 177.1$. The ion XXXV-c corresponding to 191$^+$ suffers two modes of fragmentation. One is the loss of 42 giving rise to a peak at 149$^+$ ($m^* 116.2$) while the second
loss of 18 results in a peak at mass 173 (m\(^+\) 156.8). The loss of 42 could be either CH\(_2\) = C = 0 or -N = C = 0. A six centred hydrogen migration in the \(\alpha\)-pyrone ring could facilitate the loss of CH\(_2\) = C = 0 from 191\(^+\) to give XXXV-d. This ion (m/e 149\(^+\)) could then lose a methyl group giving XXXV-e (149\(^+\) \(\rightarrow\) 134\(^+\), m\(^+\) 120.6). Alternative loss of 28 from 149\(^+\) to give 121\(^+\) is indicated by m\(^+\) 98.26 and this can be formulated as the ion XXXV-f. The loss of water occurring from 191\(^+\) as a side reaction would involve a hydrogen migration either as XXXV-d or as XXXV-g. The resulting hydroxyl group could pick up another hydrogen from the molecule to lose water. It is difficult to decide which hydrogens are incorporated in this process without proper deuteration reactions.

There are no metastable peaks to indicate the fate of the remaining fragments with low mass but all of them are consistent with the structure XXXV.
XXXV-a

\[
\text{XXXV-a} \Rightarrow XXXV-b \Rightarrow m/e 206^+
\]

\[
\text{XXXV-d} \Rightarrow XXXV-c \Rightarrow m/e 191^+
\]

\[
\text{m/e 149} \Rightarrow \text{m/e 134} \Rightarrow m/e 121 \Rightarrow ? \Rightarrow \text{m/e 191}
\]

XXXV-g
Two possible mechanisms can be considered for the formation of the compound XXXV from the α-ketonitrone XXV. The isomerisation of the nitrone and the acetylation of the ketone can take place either independently or as consecutive steps in one reaction sequence.

In the first case (1), the α-pyrone ring could be formed through a direct α-acylation by the condensation of the activated acetic anhydride at the α-carbon atom and the subsequent cyclization of the condensed product.

The stage at which migration of the nitrone oxygen occurs is probably not critical.

The alternative mechanism (2) consists of the O-acylation of the nitrone group as the first step (A) followed by conversion to a lactim
intermediate through a cyclic transition state (B and C). Such a mechanism has been suggested by Bockelheide for the formation of 2-pyridone from pyridine-N-oxide and acetic anhydride. This intermediate then undergoes condensation with C-3 carboxyl group of the nitrone to give a \( \Delta^{\gamma\delta} \)-butenolide structure (D). The nucleophilic attack of the acetate ion on this lactone intermediate could result in the cleavage of the five membered ring to an amide (E). The acyl residue at 3-position of the nitrone could then undergo condensation again at 4-position to give the \( \alpha \)-pyrone ring (F).

In other words, the acyl residue is depicted as migrating around the ring in three stages, probably involving cyclic intermediates.

Both mechanisms are theoretically conceivable and there is little evidence to permit a decision between them. It would seem likely that the
presence of the nitrone group would enhance the electrophilic reactivity of the carbonyl group which in turn would enhance the reactivity at the 4 position of the molecule. Although the isomerisation of the nitrone which occurred here was an expected reaction, the condensation of the ketone with the acylating agent was not anticipated. It appeared from an experiment carried out later in connection with the compound XXXVIII (Page 98) that the nitrone group may activate the carbonyl group to undergo such a condensation; and for this reason, the first step in the reaction of the nitrone XXV with acetic anhydride may well be acylation at position 4 and subsequent cyclization according to the mechanism (1).

**Formation of the yellow compound XXXVIII from nitrone XXV.**

When the nitrone was treated with acetic anhydride in presence of an acid catalyst, the acylation of the molecule took place as described above. However, when acetone was present in the reaction mixture, a different product (XXXVIII) was obtained.

The preparation of the compound XXXVIII using D$_6$ acetone, and its oxidation to the compound XXXX suggested that the formation of the compound involve a condensation of acetone with the 3-carbonyl group of the nitrone. It is possibly significant that acylation at position 4 does not occur in the compound XXXVIII despite the presence of a more reactive methylene component than the carbonyl group of the nitrone.

\[
\text{CH}_3 \quad \overset{\text{C}}{-}\quad \text{CH}_3
\]

is a more reactive methylene component than

\[
\text{CH}_3 \quad \overset{\text{C}}{-}\quad \text{O} \quad \text{CH}_3
\]

thus is assumed to condense with \( \overset{\text{C}}{-}\overset{\text{C}}{\text{O}} \) of the nitrone much more readily.

Once this reaction has occurred, the compound XXXV evidently cannot be formed. The acid catalysed condensation of acetone and isopropenyl acetate at the carbonyl group of the nitrone could be formulated as follows.
In this case, the isomerisation of the nitrone could have proceeded as an independent reaction-step (probably the last). In an attempt to establish the reaction sequence, the oxidation product XXX was subjected to condensation with acetone, which should lead to the formation of XXXVIII. The desired reaction did not take place either with acid or base catalysts, suggesting that the driving force for these condensation reactions of the carbonyl group is the presence of the conjugated nitrone. The isomerisation of the nitrone group would then be expected to proceed only as a final step. The nitrone was reacted with acetone alone in presence of acid and base catalysts. The acid catalysed reaction gave a very small amount of a mixture of products together with a large portion of unreacted nitrone. The red coloured mixture of products was so little that separation was not possible. However, the absorption in the infra-red region (1670, 1610, 1546 cm^{-1}) suggested the presence of the nitrone group together with C = C band and a carbonyl group.

The base-catalysed reaction gave, surprisingly, the same yellow
compound XXXVIII. The nitrone rearrangement evidently having taken place, this could be explained on the basis of nucleophilic attack by OH on the nitrone (cf. p. 1). Such a nucleophilic attack at the 2-position of the nitrone would result in a hydroxylamine which would be expected to undergo dehydration as depicted below. The acidity of the 2-hydrogen (CO - C = C - C - H) and the conjugated nature of the product both assist this reaction.

This explains why these α-ketonitrones are unstable in base, such rearrangement should lead to the 2,3 diketone (e.g. XXX from the nitrone XXV) which could polymerise very easily under base catalysis. (e.g. The compound XXX on refluxing with acetone and base did not give the yellow compound XXXVIII but a dark coloured intractable product which was not investigated further). However, in the presence of acetone, the carbonyl group of XXV, activated by the presence of the nitrone, evidently condenses more rapidly with acetone and subsequent nucleophilic attack at position 2 results than in the formation of XXXVIII.

This reaction gave further support to the assumption that condensation of acetone on 3-position of the nitrone might be the first step in the reaction with acetone and acetic anhydride.
Acid catalysed reaction of the nitrone XXV with methyl acetoacetate

The first step in the acid catalysed reaction of the nitrone with methylacetoacetate could be a condensation of the active methylene group with C-3 carbonyl group of the nitrone in a manner similar to what happens in reactions discussed previously.

The product of this condensation evidently loses the acyl group to give the α,β-unsaturated ester XXXIX, together with a second product XXXV (Page 50). The formation of XXXV indicated that such a loss was accompanied by the apparent migration of the acyl group to the 4-position of the nitrone. The γ-acyl-α,β-unsaturated ester (XXXIX-b) resulting from this migration could cyclize in the presence of an acid catalyst to the compound XXXV. The possibility of intramolecular migration of an acylation to the 4-position of the nitrone has been outlined on Page .

However, the migration need not necessarily be intramolecular. An intermolecular migration involving transacylation by a second molecule of the β-keto ester is perhaps more likely. The enol acetate could provide the requisite acyl cation for both the isomerisation of the nitrone and the attack of C-4 position to form the compound XXXV. The migration of an acyl group would not be expected to take place in the yellow compound XXXVIII, where the activating influence of the second carbonyl is not present and, moreover, cyclisation of the product is not feasible. This was in accord with the observed experimental results. Formation of α-pyrone ring systems by acid catalysed condensation of β-keto esters is well known. An instance is the synthesis of dehydrohawain effected by Macierewicz.
The base catalysed conversion of the compound XXXV to the yellow compound XXXVIII

The formation of the yellow compound XXXVIII from the α-pyrone XXXV (p. 45) was unexpected. The action of base on XXXV should have resulted in the opening of the α-pyrone ring to give an unsaturated carboxylic acid. As the yellow compound XXXVIII, which is the product of the reaction, is not a carboxylic acid, it appears that decarboxylation has also taken place and this is confirmed by chemical analysis.

The decarboxylation and the formation of the yellow compound XXXVIII from the intermediate diene carboxylic acid (S) can be explained only on the basis of a molecular rearrangement. The structure of the γ-acyl unsaturated carboxylic acid (S) suggests that a migration of the acetyl group to the α position is involved in the formation of the compound XXXVIII. The mechanism for this acyl migration (which must be intramolecular) could be envisaged as proceeding through four membered ring (T), followed by concerted band formation and band fission. The transition state could be attained by two different pathways - a concerted decarboxylation, band formation and band fission outlined as path (A), or the formation of an enolate anion (S') by the action of base on the intermediate acid which would lead to such acyclic transition state as outlined in (13).
The endate anion produced from the diene carboxylic acid (S') can have a high degree of resonance stabilization as the negative charge would be distributed over more than one centre. Thus the system facilitates overlapping of the two π-orbitals of the diene carboxylic acid (S) with subsequent delocalization. The confirmation of the molecule is probably such that the interaction between C-atoms at α and δ positions is possible and the electrophilic and nucleophilic character (respectively) of these two centres would be expected to aid in the formation of a 4-membered transition state.

The collapse of the intermediate to products evidently favours a 1 → 3 shift of the acyl portion of the molecule. This could well be due to dicarboxylation of the resultant ketoacid; in fact, the alternative mechanism (B) would regard the decarboxylation as the initiating step. Such a process would obviate the difficulty of postulating generation of a generation of a carbonium adjacent to COO⁻.

Only a few instances of such intramolecular 1,3 shifts have been reported in the literature. This type of rearrangement resembles the ready acyl migrations characteristic of acylaminoalcohols and acylaminophenols. Though a number of such reactions were considered as proceeding by an
intramolecular process, in a critical study of the mechanisms of these reactions Wiberg\textsuperscript{76} pointed out that most of them apparently involve a radical chain reaction. Only a few reactions such as the rearrangement of the phenylimino ethers\textsuperscript{77}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.7\textwidth]{structure1.png}};
\end{tikzpicture}
\end{center}

and the formation of 1,3 diketones from enol esters\textsuperscript{78}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.7\textwidth]{structure2.png}};
\end{tikzpicture}
\end{center}

allow intramolecular migration through cyclic transition states. Formation of ketones from enol carboxylates was studied by Allan et al\textsuperscript{79} an analogous acyl migration was found to occur when the end esters were irradiated.\textsuperscript{80} The latter rearrangements, being intramolecular, a cyclic transition state similar to that postulated in thermal reactions was considered. However, the fact that similar acyl migration occurs in the enolacetate (II) when the double band is fully substituted suggests that acetyl radicals could be intermediates.
The molecule (II) in this case cannot assume the orientation required for a four centre reaction because of the hindrance due to the vinyllic methyl group.

Curtin and his co-workers have recently reported a few examples of 1,3 shifts. The rearrangement of benzeneazotri:benzoylmethane I, either to the enol benzoate II, or to the hydrazone III represents a migration of the benzoyl group from O to N atoms so places that a 1,3 shift is involved. 

Although these 1,3 shifts are commonly postulated on the basis of theoretical analysis and photolysis, involving the excited state, ground state molecules may also...
Though the shift can be of intramolecular nature involving a cyclic transition state as in previous cases, the effects of substituents on the migration group and other considerations of the stereoelectronics of the molecular mechanism are not in favour of such an explanation. These authors concluded that although the four centre molecular mechanism cannot be ruled out, an ion pair or pair of free radicals could be the intermediate. However such a transition state has been described by these authors in the case of the rearrangement of isoimides to imides. The facile rearrangement of isoimides to imides is such that the former type of compounds are rarely encountered. The authors have proposed a mechanism for this rearrangement involving a 1,3 benzoyl migration through a cyclic transition state. Formation of such cyclic intermediates is facilitated in those isoimides in which the interconversion between \textit{syn}- and \textit{anti}-forms is possible, because only the \textit{syn}-form can form the proposed cyclic transition state. This is consistent with the observation that the rearrangement does not take place in molecules where such an intermediate is not possible.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{COO} & \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{COO} \\
\text{C} & = \text{N} \\
A_r \quad A_{\omega} \\
\end{align*}
\]

\[
\begin{align*}
\text{C} & = \text{N} \\
\text{C}_6\text{H}_5\text{COO} & \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{COO} \\
\text{C} & = \text{N} \\
A_r \quad A_{\omega} \\
\end{align*}
\]

Although these 1,3 shifts are commonly postulated pyrolysis and photolysis, involving the excited states, ground state molecules may also
involve such intermediates when the reactions are catalysed by acids or bases.

The main requirement of the 1, 3 shift seems to be the ability of the system to acquire the four centre transition state, with subsequent concerted collapse (i.e. band formation and fission). Such a transition state could be attained in the present instance (in the compound XXXV) as a result of concerted decarboxylation. The base catalysed migration in XXV would normally be expected to be reversible - product ratio being thermodynamically controlled. However, the intervention of a decarboxylation step (whether initial or subsequent) apparently prevents reversal. The failure to observe acyl migration in the product XXXVIII is no doubt due to the lesser stabilization of the final carbanion XXXVIII - S' as compared to XXXV - S'.

\[
\begin{align*}
    & \text{XXXVIII - S'} \\
    & \text{XXXV - S'}
\end{align*}
\]
EXPERIMENTAL

General

The micro-analyses recorded have been performed by the Australian Micro-analytical service, under Dr. K.W. Zimmerman. All melting points have been determined using an Electrothermal melting point apparatus and are corrected. Infra-red spectra were measured in Nujol mulls on Unicam SP200 machine with polystyrene film as reference. For ultraviolet spectra dilute (90 per cent) ethanolic solutions of the compounds were used; these were recorded on a Beckman DK-2A ratio recording spectrophotometer, using 1 cm quartz cells. Mass spectra were kindly measured by Dr. C.S. Barnes, C.S.R. Laboratory, Sydney.

The NMR spectrum run on a Varian A60 machine was done by Dr. S. Sternhell while the rest of them were recorded by Mr. Nicholls on a 60MC Perkin-Elmer R.10 instrument with T.M.S. as standard.
Step 1: Preparation of 5-methyl nitrohexanone-2

Methylvinyl ketone (47 g) in methanol was added dropwise to a solution of 2-nitropropane (75 g) in 120 ml methanol containing about 3 g metallic Sodium. The mixture was stirred for one hour keeping the temperature constant at 60°. After stirring for another hour, the solution was left overnight. 9 ml acetic acid was added to the reaction mixture and ether extraction carried out after evaporating the alcohol. The ether layer was washed with saturated bicarbonate solution and dried with anhydrous Na₂SO₄. On evaporating the solvent, a yellow oily liquid was obtained. Yield: 65.345 g - 56 per cent.

Step 2: Reduction of the nitroketone to 2:5:5-trimethyl-Δ¹-pyrroline 1-oxide.

Nitroketone (140 g) was stirred with 35 g NH₄Cl and 1935 ml water, keeping the temperature below 30°. 175 g Zn dust was added in small portions while stirring. Stirring was continued until the oily layer on top disappeared. The precipitated Zn oxide was filtered and washed with water. The aqueous layer was washed with 200 ml Petroleum ether (b.p. 60°-80°) to extract any unreacted compound. The water layer was separated and evaporated to a thick syrup under reduced pressure. After addition of chloroform, the solution was filtered, dried and evaporated. The nitroene was distilled under reduced pressure. Yield: 56.4 g (41.13%), b.p. 54° under 0.2 mm.

Step 3: Oxidation of 2:5:5-trimethyl-Δ¹-pyrroline 1-oxide

6.75 g 2:5:5-trimethyl-Δ¹-pyrroline 1-oxide was refluxed for 1 1/2 hours with 5.9 g SeO₂ and 45 ml methanol. After removing the precipitated Selenium, the solution was evaporated to a thick syrup. 45 ml N HCl was added to the filtrate and heated for 30 min. The precipitated Se was filtered and the filtrate extracted with ether for 10 hours. The ether
solution was dried, purified by running through a 4" column of alumina and evaporated. A red sticky solid was obtained on adding petroleum ether (40°-60°). A pure sample was obtained by chromatographing twice through Silica gel. Light yellow crystals were obtained on sublimation.

\[ \text{3.4 g (45.04%)} \] m.p. 56.4°; (Found: C, 59.49; H, 7.78; N, 9.46.

C7H11O2N requires C, 59.6; H, 7.9; N, 9.9%).

\[ \lambda_{\text{max}} \text{ 273 } \mu \text{ (e 18000)}; \]

\[ \nu_{\text{max}} 3010 \text{ cm}^{-1}, 1663 \text{ cm}^{-1} \text{ and } 1524 \text{ cm}^{-1} \]

Preparation of the 2:4-dinitrophenylhydrazone

316 mg of the above nitrone in 50 per cent ethanol (15.8 ml) was treated with an ethanolic solution of 2:4-dinitrophenylhydrazone (500.4 mg), Con. H2SO4 (1.58 ml) and water (2.53 ml). Red crystals appeared after a few minutes. The compound was recrystallized from chloroform and alcohol. It was then filtered, dried and weighed. Yield: 598 mg, m.p. 230°; (found: C, 48.47; H, 4.83; N, 21.57. C13H15O5N requires C, 48.6; H, 4.7; N, 21.8), \[ \nu_{\text{max}} \text{(Nujol)} 3070 \text{ cm}^{-1}, 1600 \text{ cm}^{-1}, \]

\[ 1545 \text{ cm}^{-1} \text{ and } 3300 \text{ cm}^{-1} \]

Preparation of the hydrazones

500 mg of the same nitrone in 30 ml benzene was treated with 1 ml anhydrous hydrazine added dropwise with stirring. After some time, excess benzene was evaporated off. Excess of hydrazine was also pumped off, to give a sticky crystalline product. The brown sticky crystals obtained were recrystallized several times from ethyl acetate. Yield: 250 mg (50%); light yellow crystals, m.p. 176.5°; (found: C, 54.42; H, 8.46; N, 26.7. C7H13N2O requires C, 54.17; H, 8.42; N, 27.08%), \[ \lambda_{\text{max}}(90/^/EtoH) \text{ 311 } \mu \text{ (e 18,500)}; \]

\[ \nu_{\text{max}} \text{(Nujol)} 1558 \text{ cm}^{-1}, 1640 \text{ cm}^{-1} \]
The hydrazone of the isomer 5,5 dimethyl - 5,6 dihydro- 3,4 (H) pyridone-1-oxide was prepared by the same procedure. In this case much care was needed both in adding the correct amount of reagents and in keeping the reaction mixture under vacuum or nitrogen. Excess of hydrazine or contact with air was found to result in decomposition products, m.p. 131.5°C, in 15 per cent yield. Found: C, 53.91%; H, 8.34%; N, 26.87%.

Preparation of the diazocompound

100 mg of the hydrazone of the α-ketonitrone XXVI in 5 ml chloroform was treated with 150 mg active MnO₂ and stirred at room temperature for one hour. A bright red solution was obtained on filtration. The chloroform solution gave in the infra-red a band at 2100 cm⁻¹ showing the presence of diazo group. Attempts to purify or concentrate the solution led to weakening of the band. The solution itself is stable only for a few hours. λ max 302 mp (ε 15,000), ν max (chloroform) 3010 cm⁻¹, 2100 cm⁻¹, 1600 cm⁻¹ and 1560 cm⁻¹.

Preparation of the 3,5-dinitrobenzoic acid ester

The diazo compound solution prepared from 100 mg hydrazone was treated with 138 mg 3,5-dinitrobenzoic acid. The clear solution was concentrated after an hour. Thin layer chromatography showed the presence of two substances, one of them being unreacted acid which was separated by chromatography in neutral alumina (10 per cent water) using chloroform as solvent. The solution was concentrated and the ester crystallized from petroleum ether (60°-80°). Yield - 190 mg (85%), m.p. 106.5°C.
Arylation of the nitron 4,5,5-trimethyl-\(\Delta^1\)-pyrrole-1-oxide with p-chlorophenyl diazonium chloride

The diazonium salt was prepared as follows; p-Chloroaniline (4 g) was dissolved in 7.2 ml hydrochloric acid and 6.2 ml water. To the above solution cooled in ice, 7.2 g ice was added followed by an aqueous solution of sodium nitrite (2.19 g in 3.1 ml water) added dropwise. The presence of excess nitrous acid was tested for with starch iodide paper. The diazonium salt solution was buffered with sodium acetate till neutral to congo red (pH 5.5-6.0).

To an aqueous solution (5 ml) of the nitron (2.52 g) were added the catalysts crystalline copper sulphate (0.078 g) and anhydrous sodium sulphite (0.125 g) followed by sodium acetate (20 g) in 23 ml water. The diazonium salt solution was added to the mixture with stirring and keeping the temperature of the reaction mixture below 10° C. Stirring was continued for an hour. A yellowish brown precipitate appeared and was filtered off at the end of the reaction. The filtrate extracted with chloroform immediately. Delay in extraction led to decomposition.

The yellowish brown precipitate was found to be a mixture of compounds by thin layer chromatography on alumina using a 1:1 mixture of chloroform and light petroleum as solvent. The second eluate fraction on evaporation gave light brown coloured crystals.

The filtrate was also found to contain the same mixture of compounds on evaporation and separation was effected by the same method. The brown
coloured crystals were then purified by repeated chromatography and sublimation. Recrystallization from light petroleum yielded light yellow prisms (m.p. 108°C; yield 1.64 g - 34 per cent) $\nu_{\text{max}}$ - 1600, 1540, 850 cm$^{-1}$; $\lambda_{\text{max}}$ 226 mp (7500), 232 (7800) and 298 mp (16,600). Found, C-65.73, H-6.97, N-5.54; C$_{15}$H$_{16}$NOCl required C-65.54, H-6.72, N-5.86%.

Preparation of the above compound from p-chlorophenyl magnesium bromide

The Grignard reagent p-chlorophenyl magnesium bromide was prepared from 1.92 g p-chlorobromobenzene in 5 ml anhydrous ether and 0.24 g of magnesium.

1.27 g nitrone (azeotropically distilled with benzene) was added dropwise to the Grignard reagent in anhydrous ether and refluxed for an hour. After cooling, the excess of Grignard reagent decomposed by aqueous ammonium chloride (5 g in 50 ml). The organic layer was separated and evaporated under reduced pressure. The residue was dissolved in ether and the ether layer was washed with water. The ether layer was concentrated and redissolved in 50 per cent of aqueous methanol (25 ml); a solution of copper sulphate (10 mg) in ammonia (2 ml; $d$ 0.880) added and air bubbled through the solution for 2 hours.

Evaporation of the reaction mixture below 60°C gave an oil and 15 ml of chloroform was added to this. The chloroform solution was washed with water, dried (Na$_2$SO$_4$) and the solution evaporated to give a crystalline compound. Chromatography on alumina using methylene - light petroleum ether mixture gave the first elution as yellow coloured solution from which the pale yellow crystalline compound was obtained in 17 per cent
yield m.p. 108°. Identified as the same compound obtained from the reaction of p-chlorobenzene diazonium chloride, by comparison of infra-red spectra and by its m.p. and mixed m.p.

Arylation with p-nitrobenzene diazonium chloride

The diazonium salt solution was prepared as before using 1.15 g p-nitroaniline and arylation of the nitrone carried out by the same procedure as the one described earlier. The dark solution containing a mixture of compounds was purified by repeated chromatography on alumina using methylene chloride as solvent. Recrystallization from methylene chloride and light petroleum ether yielded yellow prisms (0.58 g - 30 per cent) m.p. 138° v_max 1600, 1540, 1520 cm^-1 λ_max 249 μ (11,410); 348 μ (12,270). (Found - C-63.1, H-6.7, N-11.02; C_{15}H_{16}N_2O required C-62.9, H-6.45, N-11.29)

Arylation of 5, 5 dimethyl - 5, 6 dihydro- 3, 4(H) pyridone-1-oxide with p-chlorobenzene diazonium chloride

The diazonium chloride solution was prepared from p-chloroaniline (0.21 g). Arylation of the nitrone (0.23 g) was carried out as before. The reaction mixture was coloured red at the end. Chromatography on alumina with methylene chloride as solvent gave a solution from which red needles were crystallized out. Repeated crystallization gave light pink coloured crystals (0.146 g - 35 per cent) - m.p. 184° v_max 740, 1543, 1600 and 1662 cm^-1; λ_max 247 μ (10,240), 303 μ (8210). Found C-62.18, H-5.52, N-5.16; C_{15}H_{14}N_0Cl required C-62.15, H-5.577, N-5.57%

Pyridine substitution in 4, 5, 5-trimethyl- Δ^4-pyrroline oxide

The diazonium salt of pyridine was prepared from 3-aminopyridine
The nitrone (1.27 g) was then arylated and the reaction mixture chromatographed and concentrated to yield a hygroscopic oil. On removing all the water in vacuo, pinkish plates appeared. Sublimation of the crystals under vacuum 100°C bath/0.3 mm gave white plates 182 mg -
9 per cent; m.p. 164°C. Freshly distilled sample gave ν<sub>max</sub> 1550, 1550, 750 cm<sup>-1</sup>. Found C-70.54, H-7.69, while C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O required C-70.60, H-7.84%. Action of potassium chromate on 5, 5 dimethyl - 5, 6 dihydro-3, 4(H) pyridone-1-oxide -

The nitrone (0.4 g) was heated with potassium chromate (0.75 g) in 10 ml of water at 100°C for two hours. A turbidity appeared after a few minutes and a precipitate settled down later. After two hours the reaction mixture was acidified and extracted with chloroform. The dried anhydrous sodium sulphate extract evaporated to give a cream coloured precipitate. The product was purified by chromatography through silica gel using chloroform as the solvent. The compound was only sparingly soluble in chloroform and was recrystallized from chloroform (0.28 g - 70 per cent) m.p. 264°C (Found C, 59.92; H, 7.09; N, 9.8%; mol. wt. 279, 281, C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O requires C, 60.0; H, 7.14; N, 10.0 per cent mol. wt. 280) ν<sub>max</sub> 3300 (very weak), 1700, 1660, 1558, 1540 cm<sup>-1</sup>; λ<sub>max</sub>, 275 µu (22,040).

Methylation of the product with diazomethane -

Diazomethane was prepared from nitrosomethyl urea by the action of aqueous potassium hydroxide and isolated as an ether solution.

An alcoholic solution to be methylated was prepared (0.02 g in 50 ml methanol). Diazomethane was added to the ice cold alcoholic solution until a light yellow colour persisted. After 30 minutes the solution was
concentrated to give a light yellow precipitate. Recrystallized from chloroform and petroleum ether. Infra-red spectrum was the same as that of the starting material indicating that no methylation has taken place.

**Acetylation**

The compound (0.02 g) in 5 ml pyridine was refluxed with 2 ml acetic anhydride for 30 minutes. A brownish yellow precipitate appeared on concentration. Infra-red spectrum showed that the compound was not acetylated.

**Reduction with potassium borohydride**

The compound (0.2 g) was suspended in 20 ml methanol and an aqueous solution of potassium borohydride (0.8 g in 25 ml) was added. Kept on a warm water bath (30-40) for an hour. Reduction took place to give a clear solution. Methanol was evaporated off and the residue extracted with chloroform. Drying and evaporating off the solvent gave a white residue. Recrystallization from chloroform and petroleum ether gave white needles (0.12 g - 60 per cent) m.p. 168°C (Found C-58.37, H - 9.63, N - 9.22. C_{14}H_{28}O_{4}N_{2} requires C - 58.31, H - 9.79, N - 9.71 per cent). ν_{max} 3300 cm\(^{-1}\). The product readily reduced alkaline triphenyl tetrazolium chloride.

**Catalytic hydrogenation of the above hydroxylamine**

The above hydroxylamine (0.1 g) was hydrogenated over pre-reduced platinum oxide (0.02 g) in ethanol (30 ml) containing 0.2 ml hydrochloric acid at 25°C, uptake of hydrogen (16 ml) being complete in 30 minutes. Filtration and evaporation of the solvent gave a white residue. Recrystallization from ethanol gave 5 hydroxy piperidine hydrochloride dimer as prisms (0.052 g - 42 per cent) m.p. 258°C (Sample dried at 115°C).
Found C - 50.39, H - 9.14, N - 8.5, Cl - 21.2. \( \text{C}_{14}\text{H}_{28}\text{N}_{2}\text{O}_2\text{HCl} \) requires C - 51.06, H - 9.118, N - 8.5, Cl - 21.6 per cent. Electrometric titration of the hydrochloride gave \( \text{pK}_{a1} = 5.65 \), \( \text{pK}_{a2} = 8.4 \) so that \( \text{pK}_a \) was 2.75 units. For comparison piperazine dihydrochloride and another dimer \( \text{C}_{14}\text{H}_{28}\text{N}_2 \) were titrated. Piperazine dihydrochloride gave a \( \text{pK}_a \) value of 4.32 (Calc. 4.14) and the other dimer gave a value of 4.34 (11.09, 6.75).

The base was isolated from the hydrochloride (0.03 g) by treating with 0.08 g of sodium bicarbonate and extracted with chloroform. The aqueous alcoholic solution of the base was treated with 1 mole of copper sulphate solution to give a purple colour indicating the formation of a complex. Attempted condensation reaction of the dimer with nucleophilic reagents

The compound (0.042 g) was dissolved in 2 ml of trifluoroacetic acid in which it was found to be readily soluble. Dinitrophenylhydrazine reagent was added. No immediate precipitation took place. Dilution of the reaction mixture resulted in a slight precipitate, which was filtered and dried. The infra-red spectrum of the product showed it to be the starting material, and therefore, no reaction had taken place.

The dimer (0.2 g) was refluxed with 0.112 g of hydrazine hydrate in ethanol for an hour. Starting material did not go into solution completely. However, the precipitate left behind at the end of the experiment was found to be different from the starting material by infra-red spectroscopy. The impure sample could not be purified further as it was insoluble in all the solvents tried. m.p. above 300°C \( \nu_{\text{max}} \) 3250, 1600, 1540 cm \(^{-1} \).
Deuterium exchange reactions of the dimer

Nuclear magnetic resonance spectra were taken of a solution of the compound in trifluoroacetic acid, in which the compound was easily soluble. Deuterated trifluoroacetic acid was prepared from trifluoroacetic acid and D₂O.

The dimer could be obtained in a pure form by sublimation at 195°C/0.03 mm.

Deuterium exchange of the dimer using a basic catalyst

The dimer (0.028 g) in pyridine (2 ml) was refluxed with 1 ml D₂O and 0.3 ml triethylamine for an hour. The reaction mixture was set aside overnight, taking proper precautions to avoid any contact with moisture. Evaporated off the solvents completely and recrystallized from chloroform and petroleum ether.

The deuterated compound did not exchange back in undeuterated trifluoroacetic acid. However, acid catalysed deuterium exchange was found to take place on dissolving the dimer in CF₃COOD + D₂O.

Dimerisation reaction using potassium ferricyanide as catalyst

The nitrone (0.1 g), sodium bicarbonate (0.12 g) and potassium ferricyanide (0.5 g) in 5 ml water were heated on a water bath for 3 hours. The solution turned to a red colour but no precipitate appeared. Extraction of the aqueous solution with chloroform gave a mixture of two compounds, which were separated by chromatography on alumina using chloroform as solvent. The first fraction collected contained the starting material. The second fraction gave a very small amount of a brown precipitate. Infra-red spectroscopy and mixed m.p. showed the compound
to be the same as that obtained by the action of potassium chromate on the nitrone. Recrystallization with chloroform and petroleum ether yielded a small amount of the same dimer (0.012 g - 6 per cent) m.p. 263°.

Acid catalysed acylation of the nitrone XXV

To an ice cold solution of the nitrone (0.4 g) in 5 ml acetic anhydride, 0.5 ml concentrated sulphuric acid was added. After 30 minutes, the reaction mixture was warmed up for two hours on a water bath at 40-60 °C. Excess solvent was evaporated off and 5 ml water added. The mixture was extracted with chloroform and the dark coloured extract washed well with water, dried and concentrated to give a semi-solid product. Chromatography on alumina with methylene chloride and light petroleum ether (10 per cent) as solvent yielded a purple coloured solution as the first eluate. This was followed by a yellow band and tarry products were left behind. The first eluate gave a crystalline product, while evaporation of the yellow solution resulted in a gum. The crystals from the first eluate were purified by sublimation and recrystallization from methylene chloride and light petroleum ether. Colourless small needles. m.p. 158° (0.038 g) 10 per cent ν_{max} 1608, 1648 and 1760 cm^{-1}; λ_{max} 323 μ (ε 9961), 277 μ (ε 10890), 235 μ (ε 8898). (Found C - 63.87, H - 6.17, N - 6.66. C_{11}H_{13}N_{0} requires C - 63.87, H - 6.27, N - 6.761 per cent).

The acylation was also carried out using BF_{3}(C_{2}H_{5})_{2} as catalyst. 0.4 g of nitrone was dissolved in methylene chloride. 4 ml of the catalyst was added to the ice cooled solution of the nitrone while stirring
vigorously. The stirring was continued for 3 hours and 100 mg of sodium acetate was added to the mixture at the end. The solution was left overnight. The excess of solvent evaporated off. Extraction and purification gave the same white crystalline compound as above in the same yield.

Hydrogenation of the acetylation product

The acetylated compound (0.042 g) was hydrogenated over pre-reduced platinum oxide (0.01 g) in ethanol. Uptake of hydrogen was fast for the initial half an hour. After one hour of hydrogenation, the solution was filtered. Evaporated off the alcohol to give white crystals. Recrystallized from methylene chloride and light petroleum ether to yield white prisms, m.p. 178° (0.034 g). 75 per cent ν_max 1600, 1660, 1743 cm⁻¹; λ_max 280 μ and 230 μ. (Found C - 63.05, H - 7.31, N - 6.84 per cent. C₇H₁₅NO requires C - 63.17, H - 7.78, N - 6.69 per cent).

Alkaline hydrolysis of the acetylation product

2N-aqueous potassium hydroxide (2 ml) was added to an alcoholic solution of the acetylated product (0.065 g) and left overnight. The resulting yellow solution was evaporated and the residue extracted with chloroform. The extract was dried and concentrated to give yellow crystals. Purified by chromatography on alumina using methylene chloride and light petroleum ether (50 per cent) as solvent. Recrystallized from petroleum ether. Large yellow crystals (0.048 g) 65 per cent, m.p. 130°C. ν_max 1580, 1620 and 1780 cm⁻¹; λ_max 382 μ (ε 9815). (Found C - 66.51, H - 8.33, N - 7.95. C₁₀H₁₅NO₂ requires C - 66.38, H - 8.29, N - 7.74 per cent).
Acid hydrolysis of the acetylation product

The acetylated product (0.025 g) was refluxed with 25 ml N hydrochloric acid for an hour. Extracted with chloroform after cooling. The extract was dried and concentrated when the starting material was recovered unchanged.

Hydrogenation of the yellow compound

The yellow compound (0.050 g) was hydrogenated over pre-reduced platinum oxide (0.010 g) in ethanol. The uptake of hydrogen was slow for the initial period but after half an hour the solution started to lose its colour. A colourless solution was left behind after 2 hours. However, filtration of the platinum and evaporation of alcohol gave a coloured oil. Recrystallization from methylene chloride and petroleum ether gave the starting material. Hydrogenation in presence of HClO₄ catalyst gave a mixture of compounds. Thin layer chromatography showed a series of spots along with the starting material. Separation of these on alumina column was attempted but no crystalline compound was obtained apart from the starting material.

Reaction with dinitrophenylhydrazine

0.010 g of the yellow compound was dissolved in water and 2 ml dinitrophenylhydrazine reagent was added. An orange coloured precipitate appeared after half an hour. However attempts to recrystallize this hydrazone exhibited a funny behaviour. The compound turned to blue as soon as the aqueous ethanol was added, although no alkaline medium was present. No compound was identified from this mixture.
Borohydride reduction of the yellow compound

A methanolic solution of potassium borohydride (0.075 g) was added to an aqueous solution of the yellow compound (0.050 g). The solution became colourless within a few minutes' time. After half an hour, alkali was added to hydrolyze the borohydride complex. Excess of the methanol was evaporated off and extracted with ether. The colourless ether solution was dried and concentrated to give an oil. Repeated crystallisation gave a very small amount of crystalline product. Since the product obtained was very soluble in water, the aqueous reaction mixture was concentrated to evaporate the water but this led to decomposition products as no crystalline material could be got on extraction from this residue. The experiment was repeated, as the yield each time was very low - only 2-3 per cent. The product gave infra-red band as follows - $v_{\text{max}} = 3200$ (broad) and $1630 \text{ cm}^{-1}$ showing the presence of a hydroxyl group and a carbonyl group. The experiment was not repeated further as there was only a short supply of the starting material.

Oxidation of the yellow compound

The yellow compound was found to decolourise bromine water as well as permanganate solution. A neutral permanganate solution was added to an aqueous solution of the yellow compound (0.1 g) till the pink colour persisted. The reaction mixture was extracted immediately with chloroform solution. The extract after drying over anhydrous Na$_2$SO$_4$ and concentration gave feathery white crystals. Recrystallised from methylene chloride and light petroleum ether, 62 mg [51 per cent] m.p. 106°. Found C - 59.55, H - 7.85, C$_7$H$_{11}$NO$_2$ required C - 59.56, H - 7.63, $v_{\text{max}} = 3250,$
Acid catalysed acylation of the nitrone XXV with isopropeneyl acetate

The nitrone (0.4 g) was refluxed with 5 ml of isopropeneyl acetate in presence of catalytic amount (5-10 mg) of p-toluenesulphonyl chloride. The colourless solution turned to yellow immediately after the refluxing started. After 2 hours a deep coloured solution was obtained. Excess of enol acetate was evaporated off under reduced pressure and the residue was treated with water. The oily mixture was extracted with chloroform several times (20 x 5 ml) to give a fluorescent red coloured organic layer. The extract was washed with bicarbonate solution and water. The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated to a thick syrupy liquid. Thin layer chromatography on alumina using methylene chloride solvent indicated the presence of a mixture of compounds along with a fluorescent yellow spot of high Rf value. Chromatography on alumina with methylene chloride and light petroleum ether solvent mixture (3:1) as the solvent, yielded a fluorescent yellow solution as the first eluate. Evaporation of this fraction gave sticky yellow semi-solid product. The second eluate from the chromatography column was yellow oily liquid while the third one contained the unreacted nitrone. The oily liquid did not give any crystalline product. The semi-solid coming out of the first fraction was purified by repeated chromatography and recrystallisation from methylene chloride and light petroleum ether. The process gave a yellow compound free from fluorescence. The infra-red spectra of the compound and the Rf value on the thin layer plate were the same as the previous yellow compound of the alkaline hydrolysis.
Melting point (128°-130°) and mixed m.p. proved that the compounds are the same (78 mg - 20 per cent).

**Reaction of the nitrone with acetone and acetic anhydride in presence of the same catalyst.**

The nitrone (0.4 g) was dissolved in 5 ml of acetone. 3 ml of acetic anhydride was added to this solution and refluxed with the same amount of catalyst as before in the previous experiment. The solution turned to a bright red colour after half an hour. The refluxing continued for an hour. Excess of the solvents were evaporated off and residue treated with water. Extraction with chloroform (20 x 5 ml) gave a red coloured solution. The chloroform extract was washed with bicarbonate solution and water repeatedly. The washed organic layer was dried over anhydrous Na₂SO₄ and evaporated. Chromatography on alumina as before gave a yellow solution as the first fraction which on evaporation gave crystalline yellow compound. Repeated recrystallisation from methylene chloride and light petroleum ether gave long yellow needles m.p. 128° (138 mg - 35 per cent). This compound was also identified as the same yellow compound obtained from alkaline hydrolysis by its infra-red spectrum and m.p. and mixed m.p.

**Deuterium labelling reactions of the yellow compound**

The nitrone (0.4 g) was refluxed with D₆ acetone and acetic anhydride with the same catalyst. The product was isolated using the same procedure as described in the ordinary acetone reaction. Only about 15 mg (4 per cent) of the product obtained which did not recrystallise as easily as the undeuterated compound. The NMR spectrum of the crude product showed that the product was the same as from ordinary acetone.
except for the absence of a signal due to a methyl group. Infra-red spectrum in nujol did not show appreciable change indicating that NH proton had probably exchanged back. After recrystallization the mass spectrum of the compound was measured.

**Base catalysed deuterium exchange reactions of the yellow compound XXXVIII**

0.1 g of the nitrone was refluxed with 3 ml of D$_2$O and 2 ml of C$_2$H$_5$OD with catalytic amount of triethylamine. After refluxing for an hour, the mixture was left overnight taking precaution not to allow contact with atmospheric air. All the solvents were evaporated off fully and extracted with methylene chloride crystallised from methylene chloride and light petrol. The NMR spectrum of this compound showed that the protons of methyl group at 3', olefinic proton at 1' and methylene proton at 4 of this compound XXXVIII had exchanged. Only the split methylene at 6.8 was present apart from NH and gem-dimethyl group protons. The doublet collapsed to a singlet on adding D$_2$O. As the spectrum was found to contain some impurity, the compound was recrystallised again by extracting from aqueous solution. The product again showed the absence of the methyl and methylene at $\delta$ 7.53 and $\delta$ 7.81 but the olefinic proton appeared back with half its original intensity showing that the proton had been exchanged back on treatment with water.

The rates of exchange of the protons at 4, 3' and 1' position were measured using pyridine as the solvent, by adding drops of D$_2$O and NaOD in the NMR tube itself and measuring spectra at intervals. The rate of the methylene protons was greater than the others in presence of a basic catalyst. The exchange at this 4 position alone was carried out in
pyridine solution by adding $D_2O$ and 2 drops of $K_2CO_3$ (0.04 mole). As soon as the signal disappeared the reaction mixture was acidified immediately using $NHCl$, till the solution was acidic to litmus. Extraction of this gave the yellow compound deuterated at the 4 position alone.

Reaction of the nitrone XXV with acetone in presence of acid or base catalysts

The nitrone (0.40 g) was refluxed in acetone (5 ml) with an aqueous solution of $K_2CO_3$ for 2 hours. The clear solution turned to yellow immediately and became dark after half an hour. The reaction was allowed to cool and evaporated the excess of acetone. The residue was extracted with chloroform. The chloroform extract was washed with bicarbonate solution and the following procedures were carried out similar to the other reaction of nitrone with acetone and acetic anhydride. Surprisingly reaction also gave the same yellow compound in 40 per cent yield. The product obtained was identified by comparison of the infra-red spectra and melting points.

Acid catalysed reaction

The nitrone (0.4 g) was refluxed with acetone (5 ml) with a small amount (15 mg) of p-toluenesulphonyl chloride for an hour. The reaction mixture turned into dark colour after initial half an hour. The product left behind was treated as before. Extraction and thin layer chromatography showed a mixture of products apart from the starting material. Chromatographed through alumina to get a red coloured elution as the second fraction. The first fraction was only a very negligible amount of oil whose IR did not give any identifiable product. IR of the
second fraction gave bands at 1670, 1610, 1580 cm\(^{-1}\) showing that the nitrone band is still there. However this fraction was still a mixture and a second chromatography on a long thin column was carried out. The whole red colour was running together always though different solvent systems were tried (Methylenechloride and petroleum ether in different ratio). \(^1\) UV of this red intractable gum gave absorption value in the region of 200 \(\mu\) (broad). This was shifted to longer wavelength 340 \(\mu\) in alkaline medium. However, no single product was isolated apart from starting material.

**Acid catalysed reaction of the nitrone XXV with methylacetoacetate**

The nitrone (0.6 g) was refluxed with excess of (12 ml) methyl acetoacetate in the presence of the same catalyst (20-30 mg). The solution was heated in a water bath with a reflux condenser. Though the boiling point of the solvent used was quite high (169\(^\circ\)) the reaction mixture appeared to start refluxing at about 70\(^\circ\) itself indicating a by-product of low boiling point had been produced during the reaction. The refluxation continued for 2 hours. Excess of the solvent was evaporated off using a high vacuum pump taking care not to increase the temperature of the reaction mixture too much (60\(^0\)-80\(^0\)/.05 mm). A small amount of a crystalline compound was found to get sublimed on the sides of the reaction flask. After removing all the solvent the residue was treated with water and extracted as before. Extract was washed and dried as in the previous cases. Thin layer chromatography using the same materials as before showed the presence of a mixture of compounds, apart from the unchanged nitrone. Chromatography on alumina using the same solvent system gave in the
first elution a light yellow crystalline compound. The compound was recrystallised from methylene chloride and light petroleum ether m.p. 98°-98° (14.2 mg - 23 per cent), νmax 1710, 1630, 1610 cm⁻¹, λmax 365 μm. Found C - 60.84, H - 7.65, N - 7.17. C₁₀H₁₅N₃O₁₁ required C - 60.91, H - 7.61, N - 7.10.

The second elution obtained in this case was a fluorescent yellow solution which on evaporation gave an oil that could not be identified as it gave a broad infra-red spectra and appeared to be as an impure by-product. The third elution gave a light yellow coloured solution which gave white crystalline compound on evaporation. The compound was recrystallised from methylene chloride and petroleum ether (52 mg - 6.8 per cent). The infra-red spectrum of this compound identified it to be the same as the white compound obtained from the acid catalysed acylation of nitrone using acetic anhydride, m.p. 156° undepressed on admixture with the latter product.

Oxidation of the above yellow compound (98° - m.p.) (XXXIX)

An aqueous solution of the above compound (0.050 g in 10 ml of water) was taken and aqueous KMnO₄ was added dropwise till the pink colour persisted. The reaction mixture was extracted immediately to get a colourless chloroform extract. Dried over anhydrous Na₂SO₄ and evaporation gave an oil. This crystallised on adding light petroleum ether to give white feathery crystals. Melting point and IR showed the compound to be the same as the previous oxidation product obtained from the other yellow compound (m.p. 130°).

Attempted condensation reactions of the oxidation product with acetone

The oxidation product XXX (0.050 g) of the yellow compounds
was refluxed with acetone (2 ml) in presence of catalytic amount of toluenesulphonylchloride for one hour. The solvent was evaporated off after refluxing, washed with water and bicarbonate solution, extracted with chloroform. The dried chloroform extract on evaporation gave white crystals. Recrystallised from methylene chloride and light petrol, the product was found to be the unchanged starting material both by m.p. and IR.

The reaction was repeated using base catalyst. The alcoholic solution was refluxed with 2 ml of N-KOH for one hour. The reaction mixture turned to grey colour after some time. After two hours, the reaction mixture was extracted with chloroform. The dried chloroform extract gave a dark gummy product on evaporation. Thin layer gave a big streak of line showing the presence of some intractable products. It was not identified further.
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